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(54) Title: BOMBESIN RECEPTOR ANTAGONISTS

(57) Abstract: Bombesin receptor antagonists are provided which are useful for the diagnosis, prevention, or treatment of male sexual dysfunction in humans and animals, female sexual dysfunction in humans and animals, anxiety and panic disorders, social phobia, depression, psychoses, sleeping disorders, memory impairment, pulmonary hypertension, lung repair and lung development disorders, cancer including prostate cancer and pancreatic cancer, hepatic porphyria, gastrointestinal secretory disturbances, gastrointestinal disorders including colitis, Crohn's disease and inflammatory bowel disease, emesis, anorexia, pain, seasonal affective disorders, feeding disorders, or pruritus. The compounds of formula (I) or pharmaceutically acceptable salts thereof: wherein k, l, m, n, X, Ar, Ar^1, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in the description.

BOMBESIN RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to chemical compounds that are bombesin receptor antagonists, to methods for the manufacture of the above compounds and to pharmaceutical compositions containing the above compounds. It also relates to the use of the above compounds in the manufacture of medicaments for the prophylaxis or treatment of a variety of disorders in animals (including humans). It further relates to methods for administration of the above compounds to patients for the prophylaxis or treatment of a variety of disorders.

BACKGROUND TO THE INVENTION

Bombesin is a 14-amino acid peptide originally isolated from the skin of the European frog *Bombina bombina* (Anastasi A., et al., *Experientia*, 1971;27:166). It belongs to a class of peptides which share structural homology in their C-terminal decapeptide region (Dutta A.S., *Small Peptides; Chemistry, Biology, and Clinical Studies*, Chapter 2, pp 66-82). At present, two mammalian bombesin-like peptides have been identified (Battey J., et al., *TINS*, 1991;14:524), the decapeptide neuromedin B (NMB) and a 23-residue amino acid, gastrin-releasing peptide (GRP). Bombesin-like immunoreactivity has been detected in mammalian brain (Braun M., et al., *Life. Sci.*, 1978;23:2721) and the GI tract (Walsh J.H., et al., *Fed. Proc. Fed. Am. Soc. Exp. Biol.*, 1979;38:2315). This, together with studies measuring mRNA levels in rat brain (Battey J., et al., *TINS*, 1991;14:524), points to the widespread distribution of both NMB and GRP in mammalian peripheral and central nervous systems. NMB and GRP are believed to mediate a variety of biological actions via acting upon the corresponding bombesin receptors (for review, see WO 98/07718).

Bombesin evokes a number of central effects, e.g. feeding, scratching and peripheral effects e.g. contraction of rat oesophagus, secretion of gastrin, through actions at a heterogeneous population of receptors (for review, see Battey J. and Wada

E., *Trends Neurosci.*, 1991;14:524-528). The BB_1 receptor binds neuromedin B (NMB) with higher affinity than gastrin-related peptide (GRP) and neuromedin C (NMC) and BB_2 receptors bind GRP and NMC with greater affinity than NMB. More recently evidence has emerged of two more receptor subtypes denoted BB_3 and BB_4 but due to limited pharmacology, little is known of their function at present. BB_1 and BB_2 receptors have a heterogeneous distribution within the central nervous system indicating that the endogenous ligands for these receptors may differentially modulate neurotransmission. Among other areas, BB_1 receptors are present in the ventromedial hypothalamus (Ladenheim EE et al, *Brain Res.*, 1990; 537:233-240).

Both males and females can suffer from sexual dysfunction. Sexual dysfunctions are relatively common in the general population (see O'Donohue W, et al, *Clin. Psychol. Rev.* 1997;17:537-566). The disorder may relate to seeking sexual behaviour (proceptivity) and/or to acceptance of sexual behaviour, accompanied by sexual arousal (receptivity). The prevalence of sexual problems is higher in populations receiving medicaments, in particular antidepressants and anti-hypertensives. A need for pharmacotherapy for sexual dysfunction is increasing, but there has been very little research effort directed at finding drugs to treat sexual dysfunction.

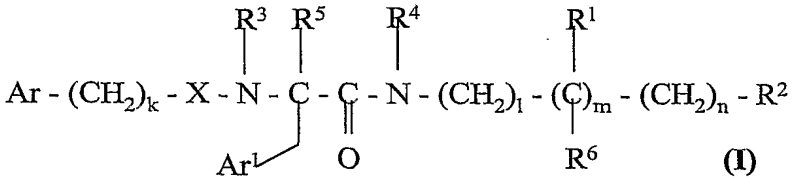
A component of male sexual dysfunction results from mechanical disorder(s), resulting in an inability to achieve penile erection or ejaculation. Treatment has been revolutionised by the unexpected discovery that cGMP PDE inhibitors, e.g. pyrazolo-[4,3-d]pyrimidin-7-ones were useful in the treatment of erectile dysfunction and could be administered orally. One such compound that is currently being manufactured is sildenafil (Viagra). However, a second component of male sexual dysfunction is psychogenic disorders. Psychogenic disorders are also more prevalent in female sexual dysfunction. Thirty to 50% of American women complain of sexual dysfunction. Ageing, menopause, and decline in circulating oestrogen levels significantly increase the incidence of sexual complaints. In a recent publication (Berman J.R. et al. , *Int. J. Impot. Res.*, 1999, 11: S31-38), the authors describe

methodology for evaluating physiologic and subjective components of the female sexual response in the clinical setting and determine the effects of age and oestrogen status on them. In a further publication (Bonney R.C et al., *Scrip's Complete Guide to Women's Healthcare*, PJB Publications Ltd, London, 2000) the causes and management of female sexual dysfunction are discussed, including the use of tibolone (Livial), which is a synthetic steroid that mimics the effects of oestrogen and has been reported to have mild androgenic properties, and the use of testosterone.

WO 98/07718 discloses a class of non-peptide compounds capable of antagonizing the effects of NMB and/or GRP at bombesin receptors. The compounds are stated to be useful in treating or preventing a variety of disorders including depression, psychoses, seasonal affective disorders, cancer, feeding disorders, gastrointestinal disorders including colitis, Crohn's disease and inflammatory bowel disease, sleeping disorders, and memory impairment. US 5,594,022 discloses non-peptide tachykinin antagonists expected to be useful in inflammatory disorders such as asthma and rheumatoid arthritis.

SUMMARY OF THE INVENTION

We have surprisingly found a further class of bombesin receptor antagonists which are compounds of formula (I) or pharmaceutically acceptable salts thereof:

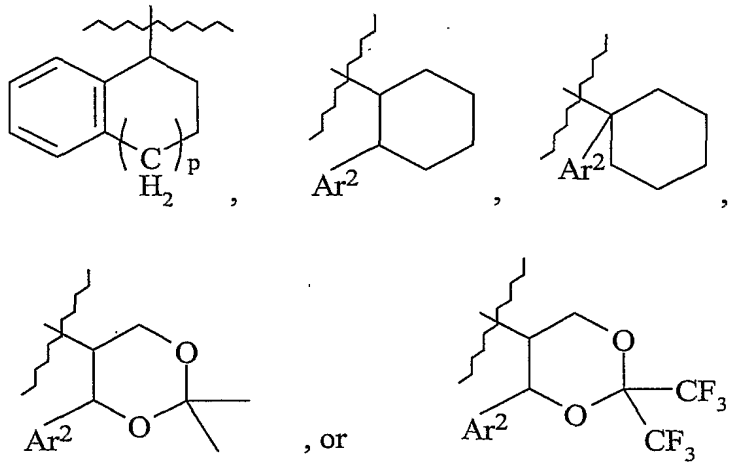


(I)

wherein:

- k is 0, 1 or 2;
- l is 0, 1, 2 or 3;
- m is 0 or 1;
- n is 0, 1 or 2;

- X is -CO-, -OCO, -SO- or -SO_2-;
- Ar is benzimidazolyl, benzofuryl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzopyrazinyl, benzotriazolyl, benzoxadiazolyl, furyl, imidazolyl, indanyl, indolyl, isoquinolyl, isoxazolyl, naphthyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrrolyl, quinolyl, tetralinyl, tetrazolyl, thiazolyl, thienyl or triazolyl each unsubstituted or substituted with from 1 to 3 substituents selected from amino, acetyl, alkyl (straight chain or branched with from 1 to 6 carbon atoms), alkoxy, cyano, halogen, hydroxy, nitro, phenyl, pyridyl, pyrrolyl, isoxazolyl, phenoxy, tolyloxy, - CF_3, -OCF_3, -SO_2CF_3, -$NHCONH_2$, -CO_2H, -CH_2CO_2H, -CH_2CN, SO_2Me, SO_2NH_2, SO_2Ph, -$(CH_2)_qNR^7R^8$, -$CONR^9R^{10}$, and CO_2R^{11}, wherein q is 0, 1 or 2 and R^7, R^8, R^9, R^{10}, R^{11} are each independently selected from hydrogen or straight or branched alkyl of up to 6 carbon atoms or cyclic alkyl of between 5 to 7 atoms which may contain 1 or 2 oxygen or nitrogen atoms or R^7 and R^8 or R^9 and R^{10} together with the nitrogen atom to which they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms;
- Ar^1 is independently selected from Ar and can also be pyridyl-*N*-oxide;
- R^1 is hydrogen or straight or branched alkyl of up to 6 carbon atoms or cyclic alkyl of between 5 and 7 atoms which may contain 1 or 2 oxygen or nitrogen atoms;
- R^2 is independently selected from Ar or is hydrogen, hydroxy, alkoxy, -NMe_2, -$CONR^{12}R^{13}$,



wherein p is 0, 1 or 2, Ar^2 is phenyl or pyridyl; and, R^{12} and R^{13} are each independently selected from hydrogen, straight or branched alkyl of up to 6 carbon atoms or cyclic alkyl of between 5 and 7 carbon atoms;

- R^3, R^4 and R^5 are each independently selected from hydrogen and lower alkyl; and
- R^6 is hydrogen, methyl or forms with R^1 a ring of from 3 to 7 carbon atoms which can contain an oxygen or nitrogen atom, or R^1 and R^6 can together be carbonyl;

provided that, when X is –OCO- , then l is 1, 2 or 3 and m is 1.

The compounds of the invention have been evaluated in receptor binding assays which measure their affinity in a cloned human NMB-preferring receptor (BB_1) assay and in a cloned human GRP-preferring receptor (BB_2) assay. It has been found that they have affinity for the BB_1 receptor and some of them also have affinity for the BB_2 receptor. Accordingly they may be useful for the diagnosis, prevention, or treatment of male sexual dysfunction in humans and animals, female sexual dysfunction in humans and animals, anxiety and panic disorders, social phobia, depression, psychoses, sleeping disorders, memory impairment, pulmonary hypertension, lung repair and lung development disorders, cancer including prostate cancer and pancreatic cancer, hepatic porphyria, gastrointestinal secretory disturbances, gastrointestinal disorders including colitis, Crohn's disease and inflammatory bowel

disease, emesis, anorexia, pain, seasonal affective disorders, feeding disorders, or pruritus.

The invention further provides a method of antagonizing the effects of neuromedin B_2 and/or gastrin-releasing peptide at bombesin receptors which comprises administering a compound of formula (I) to a patient.

The invention further provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) together with at least one pharmaceutically acceptable carrier or excipient.

The invention further provides a method for preventing or treating various diseases amenable to therapy by a bombesin receptor antagonist, including male or female sexual dysfunction, anxiety and panic disorders, social phobia, depression, psychoses, sleeping disorders, memory impairment, pulmonary hypertension, lung repair and lung development disorders, cancer including prostate cancer and pancreatic cancer, hepatic porphyria, gastrointestinal secretory disturbances, gastrointestinal disorders including colitis, Crohn's disease and inflammatory bowel disease, emesis, anorexia, pain, seasonal affective disorders, feeding disorders, or pruritus, said method comprising administering to a patient in need of such treatment an effective amount of a bombesin receptor antagonist of Formula (I).

The invention yet further provides the use of a compound of Formula (I) in the manufacture of a medicament for preventing or treating various diseases amenable to therapy by a bombesin receptor antagonist, including male or female sexual dysfunction, anxiety and panic disorders, social phobia, depression, psychoses, sleeping disorders, memory impairment, pulmonary hypertension, lung repair and lung development disorders, cancer including prostate cancer and pancreatic cancer, hepatic porphyria, gastrointestinal secretory disturbances, gastrointestinal disorders including colitis, Crohn's disease and inflammatory bowel disease, emesis, anorexia, pain, seasonal affective disorders, feeding disorders, or pruritus.

DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

The compounds of Formula (I) are optically active. The scope of the invention therefore also includes:

- All stereoisomers of the compounds of Formula (I).
- Their solvates, hydrates and polymorphs (different crystalline lattice descriptors) of the compounds of Formula (I).
- Pharmaceutical compositions of compounds of formula (I).
- Prodrugs of the compounds of Formula (I) such as would occur to a person skilled in the art, see Bundgaard, et al., *Acta Pharm. Suec.*, 1987;24:233-246.

The lower alkyl groups contemplated by the invention include straight or branched carbon chains of from 1 to 6 carbon atoms, except where specifically stated otherwise. They also include cycloalkyl groups, which are cyclic carbon chains having 3 to 7 carbon atoms, except where specifically stated otherwise, and which may be substituted with from 1 to 3 groups selected from halogens, nitro, straight or branched alkyl, and alkoxy.

The alkoxy groups contemplated by the invention comprise both straight and branched carbon chains of from 1 to 6 carbon atoms unless otherwise stated. Representative groups are methoxy, ethoxy, propoxy, *i*-propoxy, *t*-butoxy, and hexoxy.

The term "halogen" is intended to include fluorine, chlorine, bromine, iodine and astatine.

The term "amine" is intended to include free amino, alkylated amines, and acylated amines.

Optical isomers and salts

The compounds of Formula (I) all have at least one chiral centre and some have multiple chiral centres depending on their structure. In particular, the compounds

of the present invention may exist as diastereomers, mixtures of diastereomers, or as the mixed or the individual optical enantiomers. The present invention contemplates all such forms of the compounds. The mixtures of diastereomers are typically obtained as a result of the reactions described more fully below. Individual diastereomers may be separated from mixtures of the diastereomers by conventional techniques such as column chromatography or repetitive recrystallization. Individual enantiomers may be separated by conventional methods well known in the art such as conversion to a salt with an optically active compound, followed by separation by chromatography or recrystallization and reconversion to the non-salt form.

Where it is appropriate to form a salt, the pharmaceutically acceptable salts include acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycoloylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, theoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc.

Preferred salts are made from strong acids. Such salts include hydrochloride, mesylate, and sulfate.

Preferred groups of compounds

In a preferred group of the compounds of Formula (I),

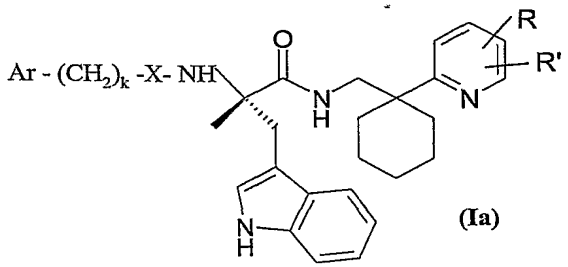
- k is 0 or 1;
- l is 1;
- m is 0 or 1;
- n is 0 or 1;

- X is -CO-, -OCO, or -SO_2-;
- Ar is benzofuryl, furyl, indolyl, isoquinolyl, naphthyl, phenyl, pyridyl, quinolyl or thienyl each unsubstituted or substituted with 1 or 2 substituents selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, - CF_3, - $(CH_2)_qNR^7R^8$, wherein R^7 and R^8 can form a ring of between 5 to 7 atoms which may contain 1 or 2 oxygen or nitrogen atoms, or R^7 and R^8 can be independently selected from hydrogen, straight or branched alkyl of up to 4 carbon atoms or cyclic alkyl of 5 carbon atoms;
- Ar^1 is independently selected from Ar, preferably indolyl, and can also be pyridyl-*N*-oxide;
- R^1 and R^6 are cyclic alkyl of from 5 to 7 carbon atoms or R^1 and R^6 together are carbonyl;
- R^2 is independently selected from unsubstituted or substituted pyridyl or is hydrogen, hydroxy, alkoxy, -NMe_2, -$CONR^{12}R^{13}$ wherein R^{12} and R^{13} are each independently selected from H and CH_3; and
- R^3, R^4 and R^5 are each independently selected from hydrogen and methyl.

In another preferred group of the compounds of Formula (I),

- l is 1;
- m is 1;
- n is 0;
- R^2 is 2-pyridyl;
- R^6 forms a cyclohexyl with R^1.

A particularly preferred group of compounds is of formula (Ia):



(Ia)

wherein Ar, k and X have the meanings given above at first, and the pyridine ring is optionally substituted by with 1 or 2 substituents, R and R', independently selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, - CF_3, -$(CH_2)_qNR^7R^8$, wherein R^7 and R^8 together with the nitrogen atom to which they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms, or R^7 and R^8 can be independently selected from hydrogen or cyclic alkyl of between 5 to 7 carbon atoms, and their pharmaceutically acceptable salts thereof.

In a further set of preferred compounds (Ia),

- Ar is benzofuryl, furyl, indolyl, isoquinolyl, naphthyl, phenyl, pyridyl, quinolyl or thienyl, each unsubstituted or substituted with 1 or 2 substituents selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, - CF_3, -$(CH_2)_qNR^7R^8$, wherein R^7 and R^8 together with the nitrogen atom to which they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms, or R^7 or R^8 can be a independently selected from hydrogen or cyclic alkyl of 5 carbon atoms, and
- X is –CO-, -OCO- or $-SO_2$.

Preferred *N*-terminal amide derivatives

Amongst *N*-terminal amide derivatives (Compounds of formula I, wherein X is -CO-) the following compounds are most preferred:

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-nitro-benzamide;

C-dimethylamino-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

1*H*-indole-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

benzo[b]thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-5-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide; and

1*H*-indole-2-carboxylic acid ((S)-2-(1*H*-indol-3-yl)-1-{[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-carbamoyl}-1-methyl-ethyl)-amide.

Other preferred *N*-terminal amide derivatives include the following:

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methyl-benzamide;

4-chloro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methoxy-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methanesulfonyl-benzamide;

3-cyano-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

3-chloro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methoxy-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methanesulfonyl-benzamide;

dimethylamino-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methyl-benzamide;

2-chloro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-nitro-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-methoxy-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-methyl-benzamide;

2-fluoro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-tolyl-ethanoylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-o-tolyl-ethanoylamino)-propionamide;

(S)-2-[2-(4-hydroxy-phenyl)-ethanoylamino]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-[2-(3-hydroxy-phenyl)-ethanoylamino]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-m-tolyl-ethanoylamino)-propionamide;

(S)-2-[2-(2-fluoro-phenyl)-ethanoylamino]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-thiophen-3-yl-ethanoylamino)-propionamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-isonicotinamide;

furan-3-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

furan-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

5-methyl-isoxazole-3-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1-methyl-1*H*-pyrrole-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

thiophene-3-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-6-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-5-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-4-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-7-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1-methyl-1*H*-indole-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

benzothiazole-6-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-benzotriazole-5-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

3-methyl-thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

5-methyl-thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

6-methyl-pyridine-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

isoquinoline-3-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

quinoxaline-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

quinoline-8-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

5-phenyl-oxazole-4-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

(S)-3-(1*H*-indol-3-yl)-2-[2-(4-methoxy-phenyl)-ethanoylamino]-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-[2-(4-dimethylamino-phenyl)-ethanoylamino]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-[2-(2-nitro-phenyl)-ethanoylamino]-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-[2-(2-methoxy-phenyl)-ethanoylamino]-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-pyrrol-1-yl-benzamide.

Preferred *N*-terminal urethane derivatives

Amongst *N*-terminal urethane derivatives (Compounds of formula I wherein X is –OC(=O)-) the following compounds are particularly preferred:

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid naphthalen-1-ylmethyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3,4-dichloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-nitro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-trifluoromethyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid quinolin-6-ylmethyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-nitro-benzyl ester; and

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-cyano-benzyl ester.

Other preferred *N*-terminal urethane derivatives include the following:

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3,4-dimethoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid naphthalen-2-ylmethyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid indan-2-yl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-methoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-chloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-fluoro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-chloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-nitro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-methyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-tert-butyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-methoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-trifluoromethyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-ethoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-cyano-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2,4-dichloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-methyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-phenoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-methyl-benzyl ester; and

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2,3-dichloro-benzyl ester.

Preferred *N*-terminal sulfonamide derivatives

Amongst *N*-terminal sulfonamide derivatives (compounds of formula I, wherein X is $-SO_2-$) the following compounds are particularly preferred:

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-phenylmethanesulfonylamino-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-chloro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(naphthalene-1-sulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(quinoline-8-sulfonylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-trifluoromethyl-benzenesulfonylamino)-propionamide;

(S)-2-(biphenyl-2-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(5-methyl-2-phenoxy-benzenesulfonyl-amino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-*p*-tolyloxy-benzenesulfonylamino)-propionamide.

Further preferred *N*-terminal sulfonamide derivatives include the following:

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(toluene-4-sulfonylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methanesulfonylamino-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-chloro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2,2,2-trifluoro-ethanesulfonylamino)-propionamide;

(S)-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(naphthalene-2-sulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(thiophene-2-sulfonylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(3-nitro-benzenesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(4-nitro-benzenesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(3-trifluoromethyl-benzenesulfonylamino)-propionamide;

(S)-2-(3,4-dichloro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(4-trifluoromethyl-benzenesulfonylamino)-propionamide;

(S)-2-(5-chloro-thiophene-2-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-chloro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(toluene-3-sulfonylamino)-propionamide;

(S)-2-(3,4-dimethoxy-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-cyano-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-cyano-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(5-chloro-1,3-dimethyl-1*H*-pyrazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(benzo[1,2,5]thiadiazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(1-methyl-1*H*-imidazole-4-sulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(benzo[1,2,5]oxadiazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

3-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethylsulfamoyl}-thiophene-2-carboxylic acid methyl ester;

(S)-3-(1*H*-indol-3-yl)-2-(5-isoxazol-3-yl-thiophene-2-sulfonylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(2-nitro-phenylmethanesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-cyano-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(1,2-dimethyl-1*H*-imidazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-(3-methoxy-benzenesulfonylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(8-nitro-naphthalene-1-sulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-chloro-5-nitro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2,4,6-trichloro-benzenesulfonylamino)-propionamide;

(S)-2-(4-chloro-2-nitro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(5-benzenesulfonyl-thiophene-2-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(4-trifluoromethoxy-benzenesulfonylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(5-methyl-2-phenoxy-benzenesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-tolyloxy-benzenesulfonylamino)-propionamide;

2-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethylsulfamoyl}-benzoic acid methyl ester;

(S)-2-(3-chloro-4-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2,5-dichloro-thiophene-3-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-chloro-4-methyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-(2-methoxy-4-methyl-benzenesulfonylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-propionamide;

(S)-2-(5-bromo-6-chloro-pyridine-3-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2,4-dinitro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-(4-methanesulfonyl-benzenesulfonylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-*tert*-butyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2,4-dichloro-5-methyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-chloro-5-trifluoromethyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(2-nitro-4-trifluoromethyl-benzenesulfonyl-amino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

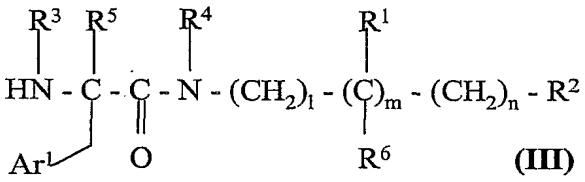
(S)-2-(4-butyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide.

Preparative methods

Compounds of the Formula (I) in which X is –CO- can be prepared by condensing an acid of the Formula (II)

$$Ar - (CH_2)_k - COOH \quad \textbf{(II)}$$

or a derivative thereof with an amine of the formula (III)



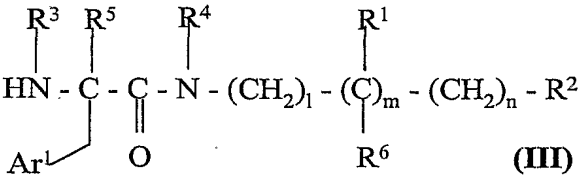
(III)

in an aprotic polar solvent in the presence of an appropriate catalyst, the values of the substituents Ar, Ar^1 and R^1 to R^6 and the parameters k to n being as defined above with reference to formula (I), and optionally converting the resulting product to a pharmaceutically acceptable salt. For example, the condensation may be carried out in DMF using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) and *N,N*-diisopropyl-ethylamine (DIPEA) as catalyst.

Compounds of the Formula (I) in which X is –O(C=O)- can be prepared by forming a carbonate from an alcohol of the Formula (IV)

$$Ar - (CH_2)_k\text{-}OH \quad \textbf{(IV)}$$

and reacting the carbonate with an amine of the Formula (III)



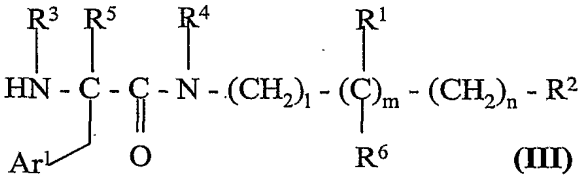
(III)

in an aprotic polar solvent in the presence of a base, the values of the substituents Ar, Ar^1 and R^1 to R^6 and the parameters k to n being as defined above with reference to Formula (I), and optionally converting the resulting product to a pharmaceutically acceptable salt. For example, the compound of Formula (IV) may be reacted with 4-nitrophenyl chloroformate in dichloromethane using pyridine as catalyst, and the resulting carbonate may be reacted with the amine of Formula (III) in dimethyl formamide using *N,N*-dimethyl-4-amino pyridine as catalyst.

Compounds of the Formula (I) in which X is $–SO_2–$ can be prepared by condensing a sulfonyl chloride of the Formula (V)

$$Ar-(CH_2)_k-SO_2Cl \quad (V)$$

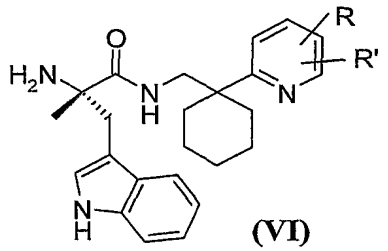
with an amine of the Formula (III)



(III)

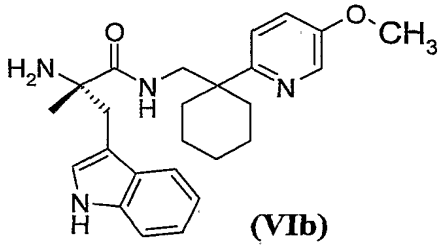
in an aprotic polar solvent in the presence of a base as catalyst, the values of the substituents Ar, Ar^1 and R^1 to R^6 and the parameters k to n being as defined above with reference to Formula (I), and optionally converting the resulting product to a pharmaceutically acceptable salt. For example, the condensation may be carried out in DMF in the presence of *N,N*-diisopropylethylamine and *N,N*-dimethyl-4-aminopyridine.

In the above methods, the amine of Formula (III) is preferably a chiral amine of Formula (VI)



(VI)

wherein the pyridine ring is optionally substituted by with 1 or 2 substituents R and R' selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, $-CF_3$, $-(CH_2)_qNR^7R^8$, wherein R^7 and R^8 together with the nitrogen atom to which they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms, or $R^7$and R^8 can be independently selected from hydrogen or cyclic alkyl of between 5 to 7 carbon atoms, methoxy being a particularly preferred substituent, as in the chiral amine (VIb):



(VIb)

This intermediate (VIb), which is (S)-2-amino-3-(1*H*-indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-propionamide, is novel.

Pharmaceutical compositions

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can comprise one or more substances that may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid that is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Liquid form preparations include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be

mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

The dosage can range from about 0.1 mmol/kg of active compound per kg of body weight to about 500 mmol/kg body weight. A preferred dosage is about 5 to about 50 mmol of active compound per kg of body weight.

Sexual dysfunction

Although there is no known direct link between the effects of bombesin receptor ligands and sexual function, the presence of receptors in hypothalamic areas might

suggest a neuromodulatory effect on functions controlled at a hypothalamic level, and these could include, among others, feeding and sexual behaviour.

Female sexual dysfunction can be grouped into four classes (Scrip's Complete Guide to Women's Healthcare, p.194-205, April 2000), which include hypoactive sexual desire disorders, sexual arousal disorders, orgasmic disorders or anorgasmy and sexual pain disorders. Hypoactive sexual desire disorders can be characterized as persistent or recurrent lack of sexual thoughts/fantasies and lack of receptivity to sexual activity, causing personal distress. Common problems include sexual aversion disorders. Sexual arousal disorders can be characterized as persistent or recurrent inability to achieve or maintain adequate sexual excitement, causing personal distress. Common problems include lack of or diminished vaginal lubrication, decreased clitoral and labial sensation, decreased clitoral and labial engorgement and lack of vaginal smooth muscle relaxation. Orgasmic disorders can be characterized as persistent or recurrent difficulty or delay in attaining orgasm after adequate sexual stimulation and arousal, causing personal distress. Sexual pain disorders can be characterized by dyspareunia, (characterised by recurrent or persistent genital pain associated with sexual intercourse), vaginismus (characterised by recurrent or persistent involuntary spasm of the muscles of the outer third of the vagina which interferes with vaginal penetration, causing personal distress) and other pain disorders (characterised by recurrent or persistent genital pain induced by non coital sexual stimulation).

The compounds of this invention are useful in the treatment of female sexual dysfunction, and this includes female sexual dysfunction associated with hypoactive sexual desire disorders, sexual arousal disorders, orgasmic disorders or anorgasmy, or sexual pain disorders.

The psychogenic component of male sexual dysfunction has been classified by the nomenclature committee of the International Society for Impotence Research (and is illustrated in Sachs B. D., *Neuroscience and Biobehavioral Review* 24: 541-560, 2000) as generalised type, characterised by a general unresponsiveness or primary lack of sexual arousal, and ageing-related decline in sexual arousability, characterised by

generalised inhibition or chronic disorders of sexual intimacy. The inventors believe that there are common mechanisms underlying the pathologies of male and female phychogenic sexual dysfunctions.

The compounds of this invention are useful in the treatment of male sexual dysfunction, especially drug induced sexual dysfunction psychogenic male sexual dysfunction associated with generalised unresponsiveness and ageing-related decline in sexual arousability.

Anxiety, panic attacks and social phobia

Anxiety is a very commonly observed symptom, for which benzodiazepines are the primary treatment agents. Chlordiazepoxide, diazepam, oxazepam, lorazepam, prazepam and alprazolam are most commonly used for this purpose in the United States. However anxiolytic benzodiazepines may also cause sedation, they have muscle-relaxant, sedative-hypnotic, and amnestic side effects; they also tend to potentiate the effects of alcohol. Some tolerance to their effects may develop, withdrawal after chronic use frequently induces rebound anxiety, and long-term use of benzodiazepines, particularly with escalating doses, can lead to dependence. Therefore there is a need for anxiolytic treatments with a reduced dependence liability.

Recent findings suggest a role of bombesin-like peptides in stress and anxiety (Plamondon H. *et al.* (1996) *Soc. Neurosci.* **22**: Abstract 181.13): antisense oligonucleotides to mRNA for GRP receptors and NMB receptors were infused i.c.v. in rats over 2 days, resulting in a reduction of bombesin binding site density in the brain, as measured by receptor autoradiography. Rats treated with the antisense oligonucleotides spent significantly more time on the anxiogenic fields of an elevated plus maze, or of a trough-tunnel oval maze, reflecting an anxiolytic effect of treatment, as compared to control animals.

The compounds of the instant invention are useful in the treatment of anxiety, panic attacks and social phobia.

Depression

The compounds of the invention are useful in the treatment of depression. The following publication provides evidences of the role of bombesin receptors in depression: Pinnock R.D., et al., *Brain Res.*, 1994;653, 199.

Psychoses

The compounds of the invention are useful in the treatment of psychoses. The following publication provides evidences of the role of bombesin receptors in psychoses: Merali., et al., *Eur. J. Pharmacol.*, 1990;191, 281.

Sleeping disorders

The compounds of the invention are useful in the treatment of sleep disorders. The following publication provides evidences of the role of bombesin receptors in sleeping disorders: Even PC., et al., *Physiol behav.*, 1991; 49(3):439-42.

Memory impairment

The compounds of the invention are useful in the treatment of memory impairment. The following publication provides evidences of the role of bombesin receptors in memory impairment: Rashidy., et al., *Brain Research.*, 1998; 814:127-32.

Pulmonary hypertension

Hurel S.J. *et al.* (*Lancet* (1996) **348**: 1243) have shown that infusion of a GRP receptor antagonist to a patient suffering from pulmonary hypertension was followed by a decrease in the pulmonary systolic pressure. The compounds of the invention are useful in the treatment of pulmonary hypertension.

Lung repair and lung development disorders

Several studies have emphasised the role of GRP and the GRP receptor in lung repair after injury and in lung development (Spurzem J.R. *et al.* (1997) *Am. J. Respir. Cell. Mol. Biol*. **16**: 209-211; Wang D.. *et al.* (1996) *Am. J. Respir. Cell. Mol. Biol.* **14**: 409-416; Spindel E.R., *Ibidem* 14: 407-408). Also, lung injury, including that induced by smoking, leads to increased levels of pulmonary bombesin-like peptides. Findings by Cutz E. et al. (*Pediatrics* (1996) **98**: 668-72) suggest that maternal smoking potentiates hyperplasia of the pulmonary neuroendocrine cells (as measured by the percentage of airway epithelium immunoreactive for bombesin) in the lungs of infants who die of sudden infant death syndrome (SIDS) and that a dysfunction of these cells may contribute to the pathophysiology of SIDS. The compounds of the instant invention are useful in the treatment of lung repair and lung development disorders.

Cancer treatment

The invention also relates to a method for treating cancer which comprises administering to a patient or a subject, particularly a mammal, more particularly a human, an effective amount of a compound of Formula (I), optionally conjugated with a cytotoxic agent. The method is particularly useful in cancers where tumour cells have a cell surface bombesin receptor, including certain prostate or pancreatic cancers.

When a directly labelled compound of Formula (I) is used for therapeutic purposes, preferably a halogen substituent of Ar as a radionuclide is used. Preferably halogen radionuclides employed for therapy are β-emitting or α-emitting radionuclides. The preferred halogen substituents of Ar for treating cancers include ^{131}I, ^{211}At, ^{76}Br and ^{77}Br, ^{131}I being particularly preferred. Compounds of Formula (I) where Ar is substituted by a radionuclide halogen can easily be prepared via electrophilic aromatic substitution of a corresponding non-radioactive compound wherein Ar is substituted by

a halide or an activating group. Such a halide is preferably Br or I. Preferred activating groups include tributyl-tin, trimethylsilyl, *t*-butyldimethylsilyl, and the like.

Conjugation of a compound of Formula (I) with a cytotoxic agent is especially preferred when, in the compound of Formula (I), R^2 is hydroxy or amino. In such a case, the compounds of the invention may conveniently be linked to a cytotoxic agent, using a bifunctional moiety like glutaric acid or the like to form a conjugate. Suitable cytotoxic agents include compounds such as doxorubicin, anticancer chemotherapy compounds such as those described in The Merck Index, 12th edition, 1996, p. MISC-10.

The use of a conjugate of a compound of Formula (I) with a radionuclide is also provided by the instant invention; preferred radionuclides used for radiotherapy emit an α or β particle; they include ^{188}Re, ^{131}I, ^{211}At, ^{212}Pb, ^{212}Bi, ^{76}Br, ^{77}Br, and the like (for examples, The Merck Index, 12th edition, 1996, page MISC-93). Said conjugates may be prepared using conventional methods. For example, radionuclides such as ^{188}Re can be linked to a compound of Formula (I) using a bifunctional chelating agent such as trisuccin (Safavy A. *et al.* (1993) *Bioconj. Chem.* **4**: 194-8) according to a process adapted from Safavy A. *et al.* in *Cancer* (1997) **80** (Suppl): 2354-9. The conjugate may take the form of a compound that is cleaved to release the cytotoxic agent on entry into the tumour cells. Compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formulae, e.g. by hydrolysis upon entry into a target cell, are preferred.

A method of the present invention for treating a mammalian tumour includes administering to a mammal a composition including a tumour-inhibiting amount of at least one compound of the present invention. Such a tumour-inhibiting amount is an amount of at least one of the subject compounds which permits sufficient tumour localisation of the compound to diminish tumour growth or size. This dosage can range from about 0.1 mmol/kg body weight to about 500 mmol/kg body weight. A preferred dosage is about 5 to about 50 mmol/kg body weight.

The amount of radioactivity administered can vary depending on the type of radionuclide. However, with this in mind the amount of radioactivity that is administered can vary from about 1 millicurie (mCi) to about 800 mCi. Preferably, about 10 mCi to about 600 mCi is administered. Moreover when considering the dosage, the specific activity of the radioactive compound should be taken into consideration. Such a specific activity is preferably very high, e.g. for ^{123}I-labelled compounds the specific activity should be at least about 1,000 Ci/mM to about 50,000 Ci/mM. More preferably the specific activity for ^{123}I-labelled compounds is, e.g., about 10,000 Ci/mM to about 22,000 Ci/mM.

a) Prostate cancer

Bombesin specifically induces intracellular calcium mobilisation via GRP receptors in human prostate cancer cells (Aprikian A.G. *et al.*(1996) *J. Mol. Endocrinol* **16**: 297-306). This suggests that the bombesin family of neuropeptides can play a regulatory role in the biology of prostate cancer. The use of antibodies raised against bombesin inhibited the growth of a prostatic carcinoma cell line (Hoosein N.M., (1993) *Cancer Bull.* **45**:436-441).

The compounds of the instant invention are useful in the diagnosis and treatment of prostate cancer.

b) Pancreatic cancer

Normal and tumour pancreatic cells contain a specific GRP receptor that is expressed more on malignant pancreatic tissues (Hajri A. *et al.*(1996) *Pancreas* **12**: 25-35). Bombesin-like peptides may stimulate proliferation of human pancreatic cancer cells (Wang Q.J. *et al. Int. J. Cancer* (1996) **68**: 528-34). As a consequence a bombesin receptor antagonist may be used to treat pancreatic cancers. Furthermore, a radiolabelled bombesin receptor antagonist may be used to treat pancreatic cancers.

The compounds of the instant invention are useful in the treatment of pancreatic cancer.

Hepatic porphyria

The major clinical manifestation of hepatic porphyrias are neurologic symptoms, including abdominal pain, neuropathy, and mental disturbances. It is believed that the neurologic symptoms are caused by an increase of a few gastrointestinal and neurotransmitter polypeptides, including GRP, in the systemic circulation during the acute phase of the disease (Medenica R. *et al.* (1997) *Cell Mol. Biol.* **43**: 9-27). Treatment with bombesin receptor antagonists may thus reduce the effects of those polypeptides that bind to bombesin receptors, and alleviate the symptomatology of acute porphyria. The compounds of the instant invention are useful in the treatment of hepatic porphyria.

Gastrointestinal secretory disturbances

GRP has proved to be a particularly valuable tool in detecting disturbances of gastric secretory function, including those associated with duodenal ulcer disease and *Helicobacter pylori* infection (McColl K.E. *et al.* (1995) *Aliment. Pharmacol. Ther.* **9**: 341-7). As a consequence, a radiolabelled bombesin receptor antagonist may be useful to diagnose these conditions. Other gastrointestinal functions such as gallbladder contraction, pancreatic secretion and gastro-oesophageal motility are subject to regulatory controls by GRP, and a radiolabelled bombesin receptor antagonist may be useful to diagnose these conditions.

The compounds of the instant invention are useful in the treatment of gastro-intestinal secretory disturbances.

Gastrointestinal disorders

The bombesin receptor has been implicated in gastric acid secretion and gastrointestinal motility Walsh J. H. *Ann. Rev Physiol* 1988; 50, 41 and Lebacq-Verheyden A *et al.*, in Handbook of Experimental pharmacology 1990;95 (part II) and references therein). As such it could be implicated in colitis, Crohn's disease and inflammatory bowel disease.

Emesis

Bombesin is present in high concentrations in the skin of frogs. As part of a defence reaction, Amphibia secrete emetic substances when swallowed by a predator.

In mammals, bombesin receptors are widely distributed in the GI tract where they cause changes in gastric motility and secretion. Bombesin receptor antagonists of the invention may decrease retching and vomiting and thus be effective in the treatment of emesis, in particular in patients receiving anticancer agents.

Anorexia

Bombesin causes a decrease of glucose intake in mice. In mice lacking the GRP receptor, bombesin no longer showed this effect (Hampton L. *et al*, *Proc. Natl. Acad. Sci. USA*, **95**: 3188-92, 1998). Bombesin receptor antagonists used in the present invention may increase feeding behavior, and thus be effective in the treatment of anorexia, such as the anorexia of cancer patients.

Pain

The compounds of the invention are useful in the treatment of pain. The following publication provides evidences of the role of bombesin receptors in pain (Cridland and Henry, *Brain Research*, 584: 163-168, 1992).

Seasonal affective disorders

The compounds of the invention are useful in the treatment of seasonal affective disorders. The following publication provides evidences of the role of bombesin receptors in seasonal affective disorders: McArthur AJ., et al., *J. Neurosci.*, 2000; 20(14):5496-502.

Feeding disorders

The compounds of the invention are useful in the treatment of feeding disorders. The following publication provides evidences of the role of bombesin receptors in feeding disorders: Ladenheim EE., et al, 1996, 54:705-711.

Pruritus

The compounds of the invention are useful in the treatment of pruritus. The following publication provides evidences of the role of bombesin receptors in pruritus: Maigret C. *et al*, *Eur. J. Pharmacol.*, 209: 57-61, 1991.

Protocol for BB_1 and BB_2 Binding Assays

In the following experiments, measurement of BB_1 and BB_2 binding was as follows. CHO-K1 cells stably expressing cloned human NMB (for (BB_1 assay) and GRP receptors (for BB_2 assay) were routinely grown in Ham's F12 culture medium supplemented with 10% foetal calf serum and 2 mM glutamine. For binding experiments, cells were harvested by trypsinization, and stored frozen at -70°C in Ham's F12 culture medium containing 5% DMSO until required. On the day of use, cells were thawed rapidly, diluted with an excess of culture medium, and centrifuged for 5 minutes at 2000 g. Cells were resuspended in 50 mM Tris-HCl assay buffer (pH 7.4 at 21°C, containing 0.02% BSA, 40 mg/mL bacitracin, 2 mg/mL chymostatin, 4 mg/mL leupeptin, and 2 mM phosphoramidon), counted, and polytronned (setting 5, 10 sec) before centrifuging for 10 minutes at 28,000 g. The final pellet was resuspended in assay buffer to a final cell concentration of 1.5×10^5/mL. For binding assays, 200 μL aliquots of membranes were incubated with [^{125}I][Tyr^4]bombesin

(<0.1 nM) in the presence and absence of test compounds (final assay volume 250 μL) for 60 minutes and 90 minutes for NMB and GRP receptors, respectively. Nonspecific binding was defined by 1 μM bombesin. Assays were terminated by rapid filtration under vacuum onto Whatman GF/C filters presoaked in 0.2% PEI for >2 hours, and washed 50 mM Tris-HCl (pH 6.9 at 21°C; 6 x 1 mL). Radioactivity bound was determined using a gamma counter.

All competition data was analysed using nonlinear regression utilising iterative curve-plotting procedures in Prism® (GraphPad Software Inc., San Diego, USA). IC_{50} values were corrected to K_i values using the Cheng-Prusoff equation (Cheng Y., Prusoff W. H., *Biochem. Pharmacol.* 22: 3099-3108, 1973).

Preparative methods

Throughout this application the following abbreviation have the meanings listed below:

NEt_3	triethylamine
THF	tetrahydrofuran
HBTU	*O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluoro-phosphate
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
TEBA	benzyltriethylammonium chloride
BOC_2O	di-*tert*-butyl dicarbonate
TFA	trifluoroacetic acid
DMA	*N,N*-dimethylacetamide
EtOAc	EtOAc
MeOH	methanol
Trp	tryptophan
Ph	phenyl
HPLC	high pressure liquid chromatography

NP	normal phase
RP	reverse phase
DMAP	*N,N*-dimethyl-4-aminopyridine
OAc	acetate
OB	oestradiol benzoate.

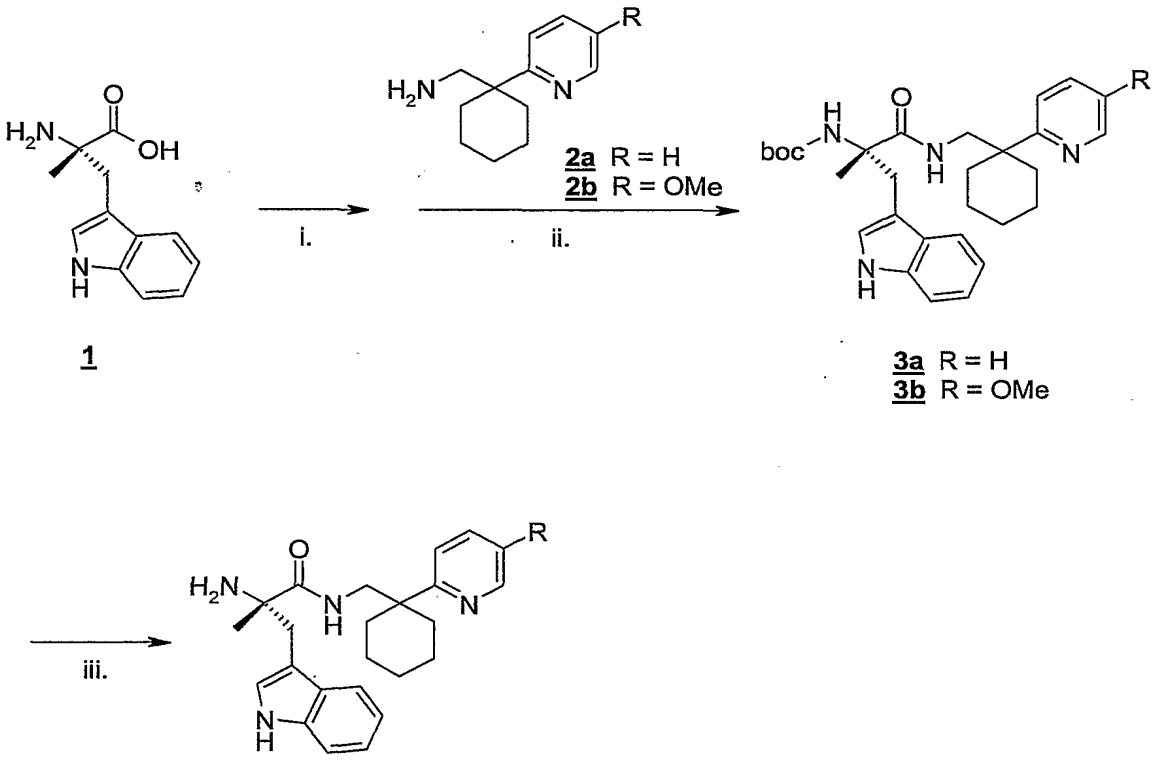
How the invention may be put into effect will now be further described with reference to the following examples.

Synthesis Example

(S)-2-Amino-3-(1 *H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide (Intermediate VIa) and **(S)-2-Amino-3-(1 *H*-indol-3-yl)-2-methyl-*N*-(1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl)-propionamide (Intermediate VIb).**

In reaction scheme 1 below, Intermediates VIa and VIb are made by (i) protecting the amino group of the starting amino acid 1 with di-*t*-butyl carbonate (BOC_2O) and potassium carbonate in dioxane/water, (ii) forming an amide by reaction of the *N*-protected amino acid with an amine 2a or 2b in dimethylformamide in the presence of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) and *N,N*-diisopropyl-ethylamine (DIPEA), and (iii) deprotecting the amino group of the product 3a or 3b by reaction with trifluoroacetic acid (TFA) in dichloromethane.

Scheme 1



i. BOC_2O, K_2CO_3, dioxane, water

ii. HBTU, DIPEA, DMF

iii. TFA, CH_2Cl_2

{(S)-2-(1-*H*-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid *tert*-butyl ester (3a)

(1) To a stirred solution of H-(S)-αMeTrp-OH (1) (10g, 46mmol) and di-t-butyl-dicarbonate (10g, 46mmol) in dioxane (100ml) was added water (20ml) and potassium carbonate (10g, 74mmol). After 4 hours the reaction mixture was acidified with 2N hydrochloric acid (150ml) and product extracted with EtOAc (2 x 200ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with EtOAc.

Removal of solvent under reduced pressure gave Boc-(S)-αMeTrp-OH as orange oil (14.5g, 99%).

(2) To a stirred solution of Boc-(S)-αMeTrp-OH (7g, 22mmol) in DMF (100ml) was added HBTU (8.0g, 22mmol), NEt_3 (5ml, 35mmol), and [1-(2-pyridyl)cyclohexyl]methylamine (**2**, 4.2g, 22mmol, described in WO 9807718). After 1 hour the reaction mixture was diluted with EtOAc (300ml) and washed with 2N hydrochloric acid (2 x 200ml), dried ($MgSO_4$) and evaporated under reduced pressure at 60°C. The residue was purified by flash chromatography. Elution with 5% methanol in dichloromethane and subsequent removal of solvent under reduced pressure gave **3a** as yellow oil (8.3g, 77%).

IR (film): 3339, 2929, 2858, 1704, 1659, 1651, 1589, 1519, 1487, 1366, 1249, 1164, 1070, 908, 737 cm^{-1};

NMR ($CDCl_3$): δ = 1.20-1.70 (20H, m), 2.00-2.12 (2H, m), 3.25-3.50 (4H, m), 5.05-5.20 (1H, br.s), 6.92 (1H, d, J=2.0 Hz), 7.02-7.32 (6H, m), 7.51 (1H, d, J=8.0 Hz), 7.59-7.64 (1H, m), 8.03 (1H, s), 8.48 (1H, d, J=4 Hz);

MS m/e (AP+): 491 (M^+ + H, 100%), 513 (M^+ + Na, 20%).

(3) **(S)-2-Amino-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexyl methyl)-propionamide (Intermediate VIa)**

To a stirred solution of **3a** (8.2g, 16.5mmol) in dichloromethane (100ml) was added trifluoroacetic acid (3.0ml, 39mmol). After 18 hours the solvent was removed under reduced pressure at 60°C. The residue was treated cautiously with saturated sodium carbonate solution (200ml) before extracting with EtOAc (3 x 200ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure at 60°C. The residue was purified by flash chromatography. Elution with 0-5% methanol in dichloromethane and subsequent removal of solvent under reduced pressure gave **Intermediate VIa** as white foam (4.85g, 75%).

MPt: 65-68°C;

IR (KBr disc): 3367, 2926, 2855, 1648, 1589, 1569, 1522, 1455, 1430, 1366, 1341, 1234, 842, 784, 742 cm^{-1};

NMR ($CDCl_3$): δ = 1.20-1.80 (13H, m), 1.98-2.20 (2H, m), 2.83 (1H, d, J=14.2 Hz), 3.33 (1H, d, J=14.2 Hz), 3.38 (2H, d, J=5.6 Hz), 6.98-7.20 (6H, m), 7.50-7.75 (3H, m), 8.05-8.15 (1H, s), 8.49-8.51 (1H, m);

MS m/e (AP+): 391 (M^+ + H, 100%).

{(S)-2-(1-*H*-Indol-3-yl)-1-methyl-1-[(1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid *tert*-butyl ester (3b)

To a stirred solution of Boc-(S)-αMeTrp-OH (1.44g, 4.5mmol) in DMF (50ml) was added HBTU (1.72g, 4.5mmol), DIPEA (2.38ml, 13.6mmol), and [1-(5-methoxy-2-pyridyl)cyclohexyl]methanamine (1g, 4.5mmol). After over night the reaction mixture was diluted with EtOAc (300ml) and water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography. Elution with EtOAc/heptane (1:1) and subsequent removal of solvent under reduced pressure gave **3b** as an oil (2.207g, 94%).

NMR ($CDCl_3$): δ = 1.24-1.60 (8H, m), 1.39 (9H, s), 1.52 (3H, s), 2.00-2.18 (2H, m), 3.20-3.43 (4H, m), 3.82 (3H, s), 6.92 (1H, d, J=2.4 Hz), 7.02-7.20 (6H, m), 7.30 (1H, d, J=6.0 Hz), 7.51 (1H, d, J=8Hz), 8.00 (1H, s), 8.17 (1H, d, J=2.8Hz).

MS m/e (ES+): 521.36 (M^+ + H, 100%), 543.25 (M^+ + Na).

Intermediate VIb

To a stirred solution of **3b** (2.2g, 4.2mmol) in dichloromethane (10ml) was added trifluoroacetic acid (5ml, excess). After stirring over night the reaction mixture was taken up in 1N HCl and extracted with diethylether. Organic phase discarded. The aqueous phase was basified cautiously with saturated sodium carbonate solution before extracting with EtOAc (3 x 50ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure at 60°C to give **Intermediate VIb** as a glass (1.253g, 71%).

IR (film): 3272, 2930, 2857, 1651, 1595, 1573, 1520, 1489, 1478, 1455, 1393, 1358, 1291, 1268, 1232, 1181, 1150, 1131, 1030, 1012, 831, 741 cm^{-1};

NMR (DMSO): δ = 1.10-1.65 (13H, m), 1.80-1.90 (1H, m), 2.00-2.10 (1H, m), 2.70 (1H, d, J=13.9 Hz), 3.10 (1H, d, J=13.9 Hz), 3.10-3.22 (2H, m), 3.77 (3H,s), 6.93-7.07 (4H, m), 7.16-7.19 (1H, m), 7.32 (1H, d, J=8.1 Hz), 7.48-7.55 (2H, m), 8.21 (1H, d, J=3.2 Hz), 10.88 (1H, s);

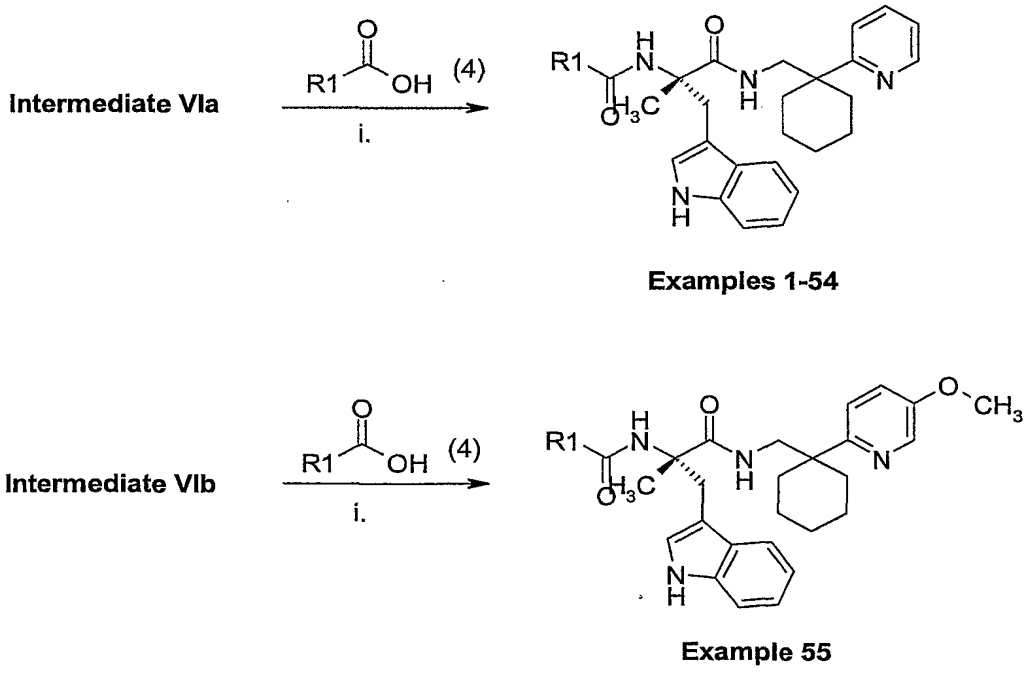
MS m/e (ES+): 421.27 (M^+ + H, 100%), 443.26 (M^+ + Na).

Examples 1-55

N-acyl derivatives of Intermediate VIa and VIb

Scheme 2 describes the synthesis of *N*-acyl derivatives of **Intermediates VIa** and **VIb**.

Scheme 2



i. HBTU, DIPEA, DMF

In scheme 2, R1 represents the rest of the carboxylic acid (4) molecule. These intermediates (4) are listed in table 1

N-acyl derivatives of Intermediate VIa

To acid **4** (0.18 mmol) was added 0.50 M HBTU in DMF (300 μL, 0.15 mmol), 1.0 M diisopropylethylamine in DMF (300 μL, 0.30 mmol) and 0.40 M **Intermediate VIa** in DMF (375 μL, 0.15 mmol). The solution was shaken on an orbital shaker at room temperature for 18 h. Water (1.0 mL) was added and the mixture was loaded onto a LC-18 SPE cartridge (0.5 g sorbent) and the cartridge was eluted with water (3 mL), 25% methanol/water (3 mL), 50% methanol/water (4 mL) and methanol (4.5 mL)). The methanol fraction was concentrated and analysed by LCMS. When the purity was <90% the product was further purified by prep. HPLC (column: Phenomenex primesphere 10 μ C18-HC 110A, 100x21.20 mm; mobile phase: methanol / water 10 to 100% gradient). The products were characterised and analysed by LCMS (column: 50x4.6 mm Prodigy ODSIII (5μ) column; mobile phase: acetonitrile / water (0.1% formic acid) 5 to 100% gradient over 2 min, held at 100% acetonitrile for 1 min; flow rate 4 mL/min; UV detection at 215 nm; mass spec: 150-900 Da full scan APCI+ centroid data)

The following products were made by the above method, with the starting material listed in Table 1 and gave the test results indicated in Table 2:

TABLE 1

Example	Intermediate 4
1	Benzoic acid
2	4-Methyl-benzoic acid
3	4-Chloro-benzoic acid
4	4-Methoxy-benzoic acid
5	4-Nitro-benzoic acid
6	4-Methanesulfonyl-benzoic acid
7	3-Cyano-benzoic acid

8	3-Chloro-benzoic acid
9	3-Methoxy-benzoic acid
10	3-Methanesulfonyl-benzoic acid
11	3-Dimethylamino-benzoic acid
12	3-Methyl-benzoic acid
13	2-Chloro-benzoic acid
14	2-Nitro-benzoic acid
15	2-Methoxy-benzoic acid
16	2-Methyl-benzoic acid
17	2-Dimethylamino-benzoic acid
18	2-Fluoro-benzoic acid
19	*p*-Tolyl-acetic acid
20	*o*-Tolyl-acetic acid
21	(4-Hydroxy-phenyl)-acetic acid
22	(3-Hydroxy-phenyl)-acetic acid
23	*m*-Tolyl-acetic acid
24	(2-Fluoro-phenyl)-acetic acid
25	Thiophen-3-yl-acetic acid
26	Pyridine-2-carboxylic acid
27	Isonicotinic acid
28	Furan-3-carboxylic acid
29	Furan-2-carboxylic acid
30	1*H*-Indole-2-carboxylic acid
31	5-Methyl-isoxazole-3-carboxylic acid
32	1-Methyl-1*H*-pyrrole-2-carboxylic acid
33	Thiophene-2-carboxylic acid
34	Thiophene-3-carboxylic acid

35	1*H*-Indole-6-carboxylic acid
36	1*H*-Indole-5-carboxylic acid
37	1*H*-Indole-4-carboxylic acid
38	1*H*-Indole-7-carboxylic acid
39	1-Methyl-1*H*-indole-2-carboxylic acid
40	Benzo[*b*]thiophene-2-carboxylic acid
41	Benzothiazole-6-carboxylic acid
42	1*H*-Benzotriazole-5-carboxylic acid
43	3-Methyl-thiophene-2-carboxylic acid
44	5-Methyl-thiophene-2-carboxylic acid
45	6-Methyl-pyridine-2-carboxylic acid
46	Isoquinoline-3-carboxylic acid
47	Quinoxaline-2-carboxylic acid
48	Quinoline-8-carboxylic acid
49	5-Phenyl-oxazole-4-carboxylic acid
50	2-Pyrrol-1-yl-benzoic acid
51	(4-Methoxy-phenyl)-acetic acid
52	(4-Dimethylamino-phenyl)-acetic acid
53	(2-Nitro-phenyl)-acetic acid
54	(2-Methoxy-phenyl)-acetic acid
55	1*H*-Indole-2-carboxylic acid

TABLE 2

Example No	Product	MH^+	Purity %	LCMS Ret time (min)	BB_1 IC50 (nM)	BB_2 IC50 (nM)
1	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide	494,64	100	1.71	2499	IA
2	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methyl-benzamide	508,67	95	1.76	2499	IA
3	4-Chloro-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexyl-methyl)-carbamoyl]-ethyl}-benzamide	529,09	94	1.84	1349	IA
4	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methoxy-benzamide	524,67	94	1.68	2879	IA
5	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-nitro-benzamide	539,64	80	1.79	343	IA
6	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methanesulfonyl-benzamide	572,73	95	1.60	2272	IA
7	3-Cyano-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide	519,65	91	1.71	2042	IA
8	3-Chloro-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexyl-methyl)-carbamoyl]-ethyl}-benzamide	529,09	97	1.84	1269	IA

9	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methoxy-benzamide	524,67	98	1.73	2859	IA
10	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methanesulfonyl-benzamide	572,73	95	1.60	3051	IA
11.	Dimethylamino-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexyl-methyl)-carbamoyl]-ethyl}-benzamide	537,71	91	1.74	2518	IA
12	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methyl-benzamide	508,67	100	1.79	2351	IA
13	2-Chloro-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexyl-methyl)-carbamoyl]-ethyl}-benzamide	529,09	98	1.79	3229	IA
14	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-nitro-benzamide	539,64	91	1.71	4581	IA
15	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-methoxy-benzamide	524,67	100	1.73	2559	IA
16	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-methyl-benzamide	508,67	100	1.79	3283	IA
17	C-Dimethylamino-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexyl-methyl)-carbamoyl]-ethyl}-benzamide	537,71	93	1.79	716	IA
18	2-Fluoro-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide	512,63	98	1.76	3949	IA
19	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-tolyl-ethanoylamino)-propionamide	522,70	94	1.76	944	IA

20	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-o-tolyl-ethanoylamino)-propionamide	522,70	98	1.76	944	IA
21	(S)-2-[2-(4-Hydroxy-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	524,67	96	1.50	3135	IA
22	(S)-2-[2-(3-Hydroxy-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	524,67	90	1.52	1437	IA
23	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-m-tolyl-ethanoylamino)-propionamide	522,70	95	1.76	817	IA
24	(S)-2-[2-(2-Fluoro-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	526,66	94	1.71	878	1546
25	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-thiophen-3-yl-ethanoylamino)-propionamide	514,70	93	1.65	1437	IA
26	Pyridine-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	495,63	98	1.68	3709	IA
27	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-isonicotinamide	495,63	98	1.47	1365	IA
28	Furan-3-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	484,60	97	1.60	1204	IA
29	Furan-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	484,60	100	1.60	1204	IA
30	1H-Indole-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	533,68	100	1.79	289	527

31	5-Methyl-isoxazole-3-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	499,62	94	1.46	4127	IA
32	1-Methyl-1H-pyrrole-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	497,65	96	1.46	4819	-
33	Thiophene-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	500,67	100	1.42	1437	IA
34	Thiophene-3-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	500,67	100	1.39	2201	IA
35	1H-Indole-6-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	533,68	100	1.42	1604	IA
36	1H-Indole-5-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	533,68	100	1.35	1881	IA
37	1H-Indole-4-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	533,68	99	1.35	4503	IA
38	1H-Indole-7-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	533,68	100	1.60	1369	IA
39	1-Methyl-1H-indole-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	547,71	100	1.70	1233	IA
40	Benzo[b]thiophene-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	550,73	100	1.63	611	IA

41	Benzothiazole-6-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	551,72	95	1.35	897	1495
42	1H-Benzotriazole-5-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	535,65	95	1.25	3167	-
43	3-Methyl-thiophene-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	514,70	100	1.53	744	IA
44	5-Methyl-thiophene-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	514,70	100	1.60	1663	IA
45	6-Methyl-pyridine-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	509,66	98	1.6	2816	IA
46	Isoquinoline-3-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	545,69	100	1.71	1363	-
47	Quinoxaline-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	546,68	94	1.67	1425	IA
48	Quinoline-8-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	545,69	96	1.57	4479	IA
49	5-Phenyl-oxazole-4-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	561,69	95	1.81	2660	IA
50	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-pyrrol-1-yl-benzamide	559,72	98	1.71	361	IA
51	(S)-3-(1H-Indol-3-yl)-2-[2-(4-methoxy-phenyl)-ethanoylamino]-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	538,70	98	1.71	1694	IA

52	(S)-2-[2-(4-Dimethylamino-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	551,74	100	1.36	2708	IA
53	(S)-3-(1H-Indol-3-yl)-2-methyl-2-[2-(2-nitro-phenyl)-ethanoylamino]-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	553,67	95	1.5	1979	IA
54	(S)-3-(1H-Indol-3-yl)-2-[2-(2-methoxy-phenyl)-ethanoylamino]-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	538,70	100	1.57	1326	2479

IA: IC50 > 10000 nM

N-acyl derivative of Intermediate VIb

Example 55

1H-Indole-2-carboxylic acid ((S)-2-(1H-indol-3-yl)-1-{[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-carbamoyl}-1-methyl-ethyl)-amide

To a solution of 1-*H*-Indole-2-carboxylic acid (38 mg, 0.24 mmol), **Intermediate VIb** (100 mg, 0.19 mmol) and diisopropylethylamine (61 mg, 0.47 mmol) in DMF (5 mL) was added HBTU (90 mg, 0.24 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with EtOAc, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (60% EtOAc/heptane) to give **Example 55** as an amorphous white solid (65 mg, 61%).

IR (film): 3285, 2931, 2855, 1651, 1537, 1489, 1456, 1420, 1342, 1310, 1267, 1028, 908, 744 cm^{-1};

NMR ($CDCl_3$): δ = 1.10-1.61 (11H, m), 1.95-2.04 (2H, m), 3.29-3.52 (4H, m), 3.43 (3H, s), 6.47 (1H,s), 6.86-6.90 (1H, m), 6.98-6.99 (2H, m), 7.09-7.42 (8H, m), 7.52-7.58 (2H, m), 7.73-7.74 (1H, m) 8.05 (1H, s), 9.11 (1H, s);

MS m/e (ES+): 564 (M^+ + H, 100%).

Binding studies of Example 55 to the bombesin receptors gave the following results (IC_{50}): BB_1: 11 nM, BB_2: 119 nM.

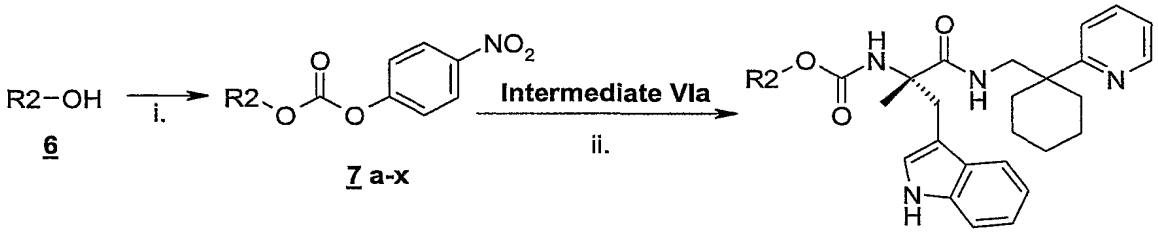
Examples 56-79

N-terminal urethane derivatives of Intermediate VIa

Scheme 3 describes the synthesis of urethane derivatives of **Intermediate VIa**:

- Conversion of alcohol into 4-nitrophenyl carbonates
- *N*-terminal urethane formation

Scheme 3



Examples 56-79

i. 4-nitrophenyl chloroformate, pyridine, THF

ii. DMAP, DMF

In scheme 3, R2 represents the rest of the intermediate (6). These intermediates (6) are listed in table 3.

To a stirred solution of alcohol 6 (10 mmol) and 4-nitrophenyl chloroformate (2.01 g, 10 mmol) in dichloromethane (50 mL) at 0°C was added dropwise a solution of pyridine (0.81 mL, 10 mmol) in dichloromethane (10 mL). The reaction mixture was allowed to slowly warm to room temperature and was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was taken up in EtOAc (50 mL) and was washed successively with 10% citric acid (2x30 mL), water (30 mL), sat. $NaHCO_3$ solution (2x50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and was concentrated under reduced pressure. The crude

product was recrystallised from typically EtOAc, diethyl ether or heptane to give pure carbonate 7. The product was characterised by IR (see Table 2 for carbonate signals).

To carbonate 7 (0.21 mmol) was added DMF (0.4 mL) followed by 0.50 M DMAP in DMF (400 μL, 0.20 mmol) and 0.50 M **Intermediate VIa** in DMF (200 μL, 0.10 mmol). The solution was shaken on an orbital shaker at room temperature for 42 h. Water (1.0 mL) was added and the mixture was loaded onto a LC-18 SPE cartridge (0.5 g sorbent) and the cartridge was eluted with 25% methanol/water (3.4 mL) and methanol (4 mL). The methanol fraction was concentrated and purified by prep. HPLC (column: Phenomenex primesphere 10 μ C18-HC 110A, 100x21.20 mm; mobile phase: methanol/water 10 to 100% gradient). The products were characterised and analysed by LCMS (column: 50x4.6 mm Prodigy ODSIII (5μ) column; mobile phase: acetonitrile/water (0.1% formic acid) 5 to 100% gradient over 2 min, held at 100% acetonitrile for 1 min; flow rate 4 mL/min; UV detection at 215 nm; mass spec: 150-900 Da full scan APCI+ centroid data).

The following products were made by the above method, with the starting material listed in Table 3 and gave the test results indicated in Table 4:

TABLE 3

Example	intermediate 6	intermediate 7: IR (cm^{-1})
56	Naphthalen-1-yl-methanol	1754
57	(3,4-Dimethoxy-phenyl)-methanol	1754
58	Naphthalen-2-yl-methanol	1752
59	Indan-2-ol	1765
60	(3,4-Dichloro-phenyl)-methanol	1754
61	(4-Methoxy-phenyl)-methanol	1748
62	(4-Chloro-phenyl)-methanol	1761
63	(2-Fluoro-phenyl)-methanol	1752
64	(2-Chloro-phenyl)-methanol	1764

65	(4-Nitro-phenyl)-methanol	1761
66	*o*-Tolyl-methanol	1757
67	(4-*tert*-Butyl-phenyl)-methanol	1766
68	(3-Nitro-phenyl)-methanol	1769
69	(2-Methoxy-phenyl)-methanol	1766
70	(4-Trifluoromethyl-phenyl)-methanol	1763
71	(3-Ethoxy-phenyl)-methanol	1767
72	3-Hydroxymethyl-benzonitrile	1769
73	(2,4-Dichloro-phenyl)-methanol	1768
74	*m*-Tolyl-methanol	1757
75	(3-Phenoxy-phenyl)-methanol	1766
76	(3-Trifluoromethyl-phenyl)-methanol	1770
77	p-Tolyl-methanol	1759
78	(2,3-Dichloro-phenyl)-methanol	1758
79	Quinolin-6-yl-methanol	1761

TABLE 4

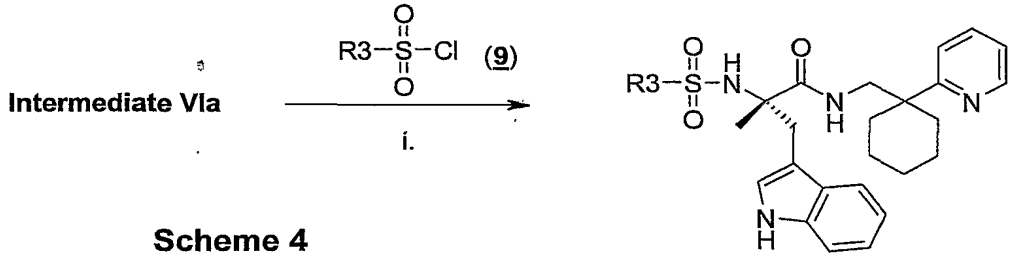
Example No	Product	MH^+	Purity %	LCMS Ret time (min)	BB_1 IC50 (nm)	BB_2 IC50 (nm)
56	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid naphthalen-1-ylmethyl ester	574,73	100	1.67	239	IA
57	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3,4-dimethoxy-benzyl ester	584,72	95	1.41	1758	IA
58	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid naphthalen-2-ylmethyl ester	574,73	100	1.67	1001	IA
59	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid indan-2-yl ester	550,71	91	1.59	955	IA

60	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3,4-dichloro-benzyl ester	593,56	93	1.73	202	IA
61	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-methoxy-benzyl ester	554,70	93	1.49	1610	IA
62	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-chloro-benzyl ester	559,11	98	1.62	681	IA
63	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-fluoro-benzyl ester	542,66	91	1.52	923	IA
64	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-chloro-benzyl ester	559,11	89	1.62	624	IA
65	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-nitro-benzyl ester	569,67	97	1.51	41	463
66	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-methyl-benzyl ester	538,70	94	11.60	751	IA
67	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-tert-butyl-benzyl ester	580,78	100	1.86	1986	IA
68	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-nitro-benzyl ester	569,67	97	1.51	17	612
69	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-methoxy-benzyl ester	554,70	96	1.52	818	IA
70	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-trifluoromethyl-benzyl ester	592,67	97	1.7	1102	IA

71	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-ethoxy-benzyl ester	568,72	89	1.60	1065	IA
72	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-cyano-benzyl ester	549,68	99	1.43	85	IA
73	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2,4-dichloro-benzyl ester	593,56	95	1.78	450	IA
74	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-methyl-benzyl ester	538,70	96	1.59	841	IA
75	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-phenoxy-benzyl ester	616,77	96	1.78	1350	IA
76	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-trifluoromethyl-benzyl ester	592,67	96	1.67	182	IA
77	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-methyl-benzyl ester	538,70	97	1.60	1084	IA
78	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2,3-dichloro-benzyl ester	593,56	94	1.73	152	IA
79	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid quinolin-6-ylmethyl ester	575,72	97	1.22	171	IA

Examples 80-137

***N*-terminal sulfonamide derivatives of Intermediate VIa**



Scheme 4

Examples 80-137

In scheme 4, R3 represents the rest of the intermediate (9). These intermediates (9) are listed in table 5

N-sulfonamide derivatives of Intermediate VIa

To sulfonyl chloride 9 (0.14 mmol) was added 0.143 M **Intermediate VIa** in DMF (700 µL, 0.10 mmol) followed by 300 µL of a solution containing a mixture of diisopropylethylamine (0.667 M in DMF, 0.20 mmol) and 4-dimethylaminopyridine (0.033 M in DMF, 0.01 mmol). The reaction mixture was shaken in an orbital shaker at 70°C for 16 h. The crude reaction mixture was loaded onto a 5 g silica cartridge and the cartridge was eluted with EtOAc in heptane (30 to 100% gradient). Removal of the solvent under reduced pressure gave the sulfonamides (**Examples 80-137**). The purity of the sulfonamide was checked by LCMS. Those samples that were less than 95% pure were further purified by prep HPLC (column: YMC-Pack ODS-AM, 5µm, 150x20 mm; mobile phase: acetonitrile / water 40 to 100% gradient). The products were characterised and analysed by LCMS (column: 150x4.6 mm Prodigy ODS3 (3µ) column; mobile phase: acetonitrile (0.085% TFA) / water (0.1% TFA) 20 to 100% gradient over 7 min, held at 100% acetonitrile (0.085% TFA) for 1 min; flow rate 1.5 mL/min; detection: diode array 200-300 nm; mass spec: 150-900 Da full scan APCI+ centroid data) (see Table 3).

The following examples were made by the above method, with the starting material listed in Table 5 and gave the test results indicated in Table 6:

TABLE 5

Example	intermediate 9
80	Phenyl-methanesulfonyl chloride
81	4-Methyl-benzenesulfonyl chloride
82	2-Chloro-benzenesulfonyl chloride
83	2-Fluoro-benzenesulfonyl chloride
84	Naphthalene-1-sulfonyl chloride
85	4-Chloro-benzenesulfonyl chloride
86	5-Dimethylamino-naphthalene-1-sulfonyl chloride
87	Naphthalene-2-sulfonyl chloride
88	Thiophene-2-sulfonyl chloride
89	Quinoline-8-sulfonyl chloride
90	3-Nitro-benzenesulfonyl chloride
91	4-Fluoro-benzenesulfonyl chloride
92	4-Nitro-benzenesulfonyl chloride
93	3-Trifluoromethyl-benzenesulfonyl chloride
94	3,4-Dichloro-benzenesulfonyl chloride
95	3-Fluoro-benzenesulfonyl chloride
96	4-Trifluoromethyl-benzenesulfonyl chloride
97	5-Chloro-thiophene-2-sulfonyl chloride
98	2-Trifluoromethyl-benzenesulfonyl chloride
99	3-Chloro-benzenesulfonyl chloride
100	3-Methyl-benzenesulfonyl chloride
101	3,4-Dimethoxy-benzenesulfonyl chloride
102	4-Cyano-benzenesulfonyl chloride
103	2-Cyano-benzenesulfonyl chloride
104	5-Chloro-1,3-dimethyl-1*H*-pyrazole-4-sulfonyl chloride
105	3,5-Dimethyl-isoxazole-4-sulfonyl chloride
106	Benzo[1,2,5]thiadiazole-4-sulfonyl chloride

107	1-Methyl-1*H*-imidazole-4-sulfonyl chloride
108	Benzo[1,2,5]oxadiazole-4-sulfonyl chloride
109	3-Chlorosulfonyl-thiophene-2-carboxylic acid methyl ester
110	5-Isoxazol-3-yl-thiophene-2-sulfonyl chloride
111	(2-Nitro-phenyl)-methanesulfonyl chloride
112	3-Cyano-benzenesulfonyl chloride
113	1,2-Dimethyl-1*H*-imidazole-4-sulfonyl chloride
114	3-Methoxy-benzenesulfonyl chloride
115	8-Nitro-naphthalene-1-sulfonyl chloride
116	2-Chloro-5-nitro-benzenesulfonyl chloride
117	2,4,6-Trichloro-benzenesulfonyl chloride
118	4-Chloro-2-nitro-benzenesulfonyl chloride
119	5-Benzenesulfonyl-thiophene-2-sulfonyl chloride
120	4-Trifluoromethoxy-benzenesulfonyl chloride
121	5-Methyl-2-phenoxy-benzenesulfonyl chloride
122	2-*p*-Tolyloxy-benzenesulfonyl chloride
123	Biphenyl-2-sulfonyl chloride
124	2-Chlorosulfonyl-benzoic acid methyl ester
125	3-Chloro-4-fluoro-benzenesulfonyl chloride
126	2,5-Dichloro-thiophene-3-sulfonyl chloride
127	3-Chloro-4-methyl-benzenesulfonyl chloride
128	2-Methoxy-4-methyl-benzenesulfonyl chloride
129	5-Pyridin-2-yl-thiophene-2-sulfonyl chloride
130	5-Bromo-6-chloro-pyridine-3-sulfonyl chloride
131	2,4-Dinitro-benzenesulfonyl chloride
132	4-Methanesulfonyl-benzenesulfonyl chloride
133	4-*tert*-Butyl-benzenesulfonyl chloride
134	2,4-Dichloro-5-methyl-benzenesulfonyl chloride
135	2-Chloro-5-trifluoromethyl-benzenesulfonyl chloride
136	2-Nitro-4-trifluoromethyl-benzenesulfonyl chloride
137	4-Butyl-benzenesulfonyl chloride

TABLE 6

Example No	Product	MH^+	Purity %	LCMS Ret time (min)	BB_1 IC50 (nm)	BB_2 IC50 (nm)
80	(S)-3-(1H-Indol-3-yl)-2-methyl-2-phenylmethanesulfonylamino-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	544,72	100	4.64	186	IA
81	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(toluene-4-sulfonylamino)-propionamide	544,72	100	4.74	557	IA
82	(S)-2-(2-Chloro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	565,14	100	4.71	257	IA
83	(S)-2-(2-Fluoro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	548,68	100	4.54	267	IA
84	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(naphthalene-1-sulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	580,76	99	4.98	185	1576
85	(S)-2-(4-Chloro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	565,14	97	4.89	373	4386
86	(S)-2-(5-Dimethylamino-naphthalene-1-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	623,82	100	4.39	1302	IA
87	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(naphthalene-2-sulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	580,76	100	5.01	322	IA
88	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(thiophene-2-sulfonylamino)-propionamide	536,72	99	4.39	232	Ia

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89	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(quinoline-8-sulfonylamino)-propionamide	581,74	99	4.53	108	IA
90	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(3-nitro-benzenesulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	575,69	99	4.58	208	1960
91	(S)-2-(4-Fluoro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	548,68	100	4.60	560	4165
92	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(4-nitro-benzenesulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	575,69	98	4.65	515	IA
93	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(3-trifluoromethyl-benzenesulfonylamino)-propionamide	599,58	100	5.03	440	2246
94	(S)-2-(3,4-Dichloro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	599,58	99	5.47	216	IA
95	(S)-2-(3-Fluoro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	548,68	100	4.65	407	2761
96	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(4-trifluoromethyl-benzenesulfonylamino)-propionamide	598,69	95	5.31	553	IA
97	(S)-2-(5-Chloro-thiophene-2-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	571,17	99	4.94	404	IA
98	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-trifluoromethyl-benzenesulfonylamino)-propionamide	598,69	99	5.11	134	-

99	(S)-2-(3-Chloro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	565,14	99	5.05	331	2687
100	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(toluene-3-sulfonylamino)-propionamide	544,72	99	4.93	393	1019
101	(S)-2-(3,4-Dimethoxy-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	590,75	98	4.50	608	IA
102	(S)-2-(4-Cyano-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	555,70	99	4.61	766	IA
103	(S)-2-(2-Cyano-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	555,70	97	4.62	408	IA
104	(S)-2-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	583,16	98	4.38	1252	IA
105	(S)-2-(3,5-Dimethyl-isoxazole-4-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	549,70	96	4.54	515	IA
106	(S)-2-(Benzo[1,2,5]thiadiazole-4-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	588,76	97	4.67	256	IA
107	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(1-methyl-1H-imidazole-4-sulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	534,69	100	3.60	3667	IA
108	(S)-2-(Benzo[1,2,5]oxadiazole-4-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	572,69	100	4.70	507	IA
109	3-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethylsulfamoyl}-thiophene-2-carboxylic acid methyl ester	594,76	100	4.79	167	IA

110	(S)-3-(1H-Indol-3-yl)-2-(5-isoxazol-3-yl-thiophene-2-sulfonylamino)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	603,77	98	4.60	534	IA
111	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(2-nitro-phenylmethanesulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	589,72	100	4.65	430	IA
112	(S)-2-(3-Cyano-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	555,70	99	4.55	460	IA
113	(S)-2-(1,2-Dimethyl-1H-imidazole-4-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	548,71	96	3.55	2482	IA
114	(S)-3-(1H-Indol-3-yl)-2-(3-methoxy-benzenesulfonylamino)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	560,72	99	4.75	295	3686
115	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(8-nitro-naphthalene-1-sulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	625,75	99	4.89	177	IA
116	(S)-2-(2-Chloro-5-nitro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	610,14	96	5.00	374	Ia
117	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2,4,6-trichloro-benzenesulfonylamino)-propionamide	634,03	100	5.45	215	Ia
118	(S)-2-(4-Chloro-2-nitro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	610,14	100	5.13	513	IA
119	(S)-2-(5-Benzenesulfonyl-thiophene-2-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	676,88	100	5.03	297	IA

120	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(4-trifluoromethoxy-benzenesulfonylamino)-propion amide	614,69	99	5.35	635	IA
121	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(5-methyl-2-phenoxy-benzenesulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	636,82	97	5.79	76	IA
122	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-tolyloxy-benzenesulfonylamino)-propionamide	636,82	97	5.79	90	IA
123	(S)-2-(Biphenyl-2-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	606,79	97	5.52	166	IA
124	2-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethylsulfamoyl}-benzoic acid methyl ester	588,73	99	4.84	242	IA
125	(S)-2-(3-Chloro-4-fluoro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	583,13	95	5.12	284	1216
126	(S)-2-(2,5-Dichloro-thiophene-3-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	605,61	99	5.23	214	IA
127	(S)-2-(3-Chloro-4-methyl-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	579,17	97	5.28	299	3939
128	(S)-3-(1H-Indol-3-yl)-2-(2-methoxy-4-methyl-benzenesulfonylamino)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	574,75	96	4.92	445	IA

129	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-propionamide	613,81	100	4.79	344	IA
130	(S)-2-(5-Bromo-6-chloro-pyridine-3-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	645,02	95	5.09	187	IA
131	(S)-2-(2,4-Dinitro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	620,69	100	4.97	475	IA
132	(S)-3-(1H-Indol-3-yl)-2-(4-methanesulfonyl-benzenesulfonylamino)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	608,78	98	4.20	1043	IA
133	(S)-2-(4-tert-Butyl-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	586,80	96	5.65	406	IA
134	(S)-2-(2,4-Dichloro-5-methyl-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	613,61	97	5.64	172	IA
135	(S)-2-(2-Chloro-5-trifluoromethyl-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	633,14	100	5.33	627	IA
136	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(2-nitro-4-trifluoromethyl-benzenesulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	643,69	100	5.34	758	IA
137	(S)-2-(4-Butyl-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	586,80	96	5.84	492	IA

Biological Examples

EXAMPLE 138 (Biological example I)

Method to test effect of compounds of formula (I) on female rat sexual proceptivity

The following method can be used to test the effect of compounds of this invention on the proceptivity of female rats. House in groups of 6 in a reversed lighting system of 12 h light:dark (lights off 7.00-19.00 h) ovariectomised adult female Sprague Dawley rats (180-200 g). Two weeks after ovariectomy the animals can be use for sexual activity tests. Adapt animals to the apparatus (in the absence of stimuli animals) for 10 min on 2 consecutive days prior to testing. Start the experiment at least 5 h into the dark period. Carry out tests in a circular arena of 90 cm diameter, surrounded by a 30 cm high wall. Two small cages with wire-mesh front (15x15 cm) are fixed into the wall such that the front of the cage is "flush" with the wall and the 2 cages are opposite each other. These will contain two stimuli animals: an intact sexually experienced male and a receptive female (ovariectomised, primed with 5 μg oestradiol benzoate dissolved in corn oil and injected subcutaneously 48 h before the test and with 0.5 mg of progesterone 4 h before the test). Sexually naïve test and control animals are used. Forty eight hours before the tests, both the test and control animals can be primed with 5 μg oestradiol benzoate. Test animals are treated with the compound(s) of formula (I) (30-100 mg/kg) dissolved in an appropriate vehicle and administered in a 1 ml/kg volume 1h before each test. For animals used as positive controls, progesterone (0.5 mg/0.1 ml) can be dissolved in corn oil and administered subcutaneously (s.c.), 4h before the test. Test and control animals are then introduced one at a time for 10-minute periods into the arena. During the 10-min test, the time that the test or positive control animal spent investigating each stimulus animal are noted. The arena should be thoroughly cleaned between animals. The position of the male/female stimuli boxes is randomised between animals, in order to avoid place preference. The difference in the percentage of time spent investigating male minus female can be calculated, out of the total time spent investigating stimuli animals. Analysis of this data will help determine if the compounds of formula (I) are beneficial in the treatment of sexual dysfunction.

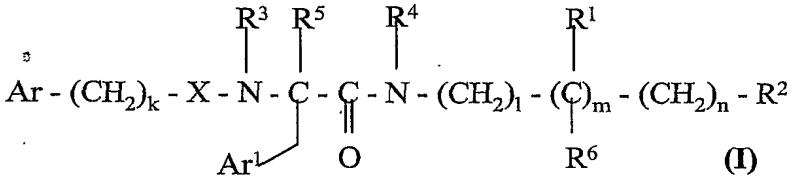
EXAMPLE 139 (Biological Example II)

Method to test effect of compounds of formula (I) on female rat sexual receptivity

The following method can be used to test the effect of compounds of this invention on the receptivity of female rats. House in groups of 6 in a reversed lighting system of 12 h light:dark (lights off 7.00-19.00 h) ovariectomised adult female Sprague Dawley rats (180-200 g). Two weeks after ovariectomy the animals can be use for sexual activity tests. The experiments should start at least 5 h into the dark period. The above compound of formula (I) can be dissolved in appropriate vehicle and administered. Quinelorane dihydrochloride (LY 163,502, 6.25 μg/kg) can be dissolved in water and administered s.c., as a positive control. Compounds can be administered in a 1-ml/kg volume. Forty eight hours before tests, the animals are primed with 5 μg oestradiol benzoate dissolved in corn oil and injected s.c. The females are then placed with a series of vigorous male rats and subjected to 10 mounts. The lordotic response of the animal is recorded and expressed as a percentage of the mounts (i.e. lordosis quotient, LQ). Treatment induced LQ = 0-10 % in most of the animals, can be considered non-receptive (NR). Animals showing higher LQ are excluded from the study. Each rat should be tested prior to administration of the compound of formula (I) and then tested similarly at 1 h and at 90 min post-injection of the above compound or quinelorane respectively. Analysis of this data will help determine if the compounds of formula (I) are beneficial in the treatment of sexual dysfunction.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:

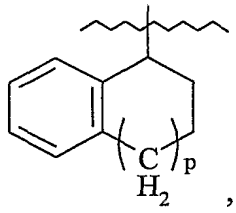


(I)

wherein:

- k is 0, 1 or 2;
- l is 0, 1, 2 or 3;
- m is 0 or 1;
- n is 0, 1 or 2;
- X is -CO-, -OCO, -SO- or $-SO_2-$;
- Ar is benzimidazolyl, benzofuryl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzopyrazinyl, benzotriazolyl, benzoxadiazolyl, furyl, imidazolyl, indanyl, indolyl, isoquinolyl, isoxazolyl, naphthyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrrolyl, quinolyl, tetralinyl, tetrazolyl, thiazolyl, thienyl or triazolyl each unsubstituted or substituted with from 1 to 3 substituents selected from amino, acetyl, alkyl (straight chain or branched with from 1 to 6 carbon atoms), alkoxy, cyano, halogen, hydroxy, nitro, phenyl, pyridyl, pyrrolyl, isoxazolyl, phenoxy, tolyloxy, - CF_3, $-OCF_3$, $-SO_2CF_3$, $-NHCONH_2$, $-CO_2H$, $-CH_2CO_2H$, $-CH_2CN$, SO_2Me, SO_2NH_2, SO_2Ph, $-(CH_2)_qNR^7R^8$, $-CONR^9R^{10}$, and CO_2R^{11}, wherein q is 0, 1 or 2 and R^7, R^8, R^9, R^{10}, R^{11} are each independently selected from hydrogen or straight or branched alkyl of up to 6 carbon atoms or cyclic alkyl of between 5 to 7 atoms which may contain 1 or 2 oxygen or nitrogen atoms or R^7 and R^8 or R^9 and R^{10} together with the nitrogen atom to which they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms;
- Ar^1 is independently selected from Ar and can also be pyridyl-*N*-oxide;

- R^1 is hydrogen or straight or branched alkyl of up to 6 carbon atoms or cyclic alkyl of between 5 and 7 atoms which may contain 1 or 2 oxygen or nitrogen atoms;
- R^2 is independently selected from Ar or is hydrogen, hydroxy, alkoxy, $-NMe_2$, $-CONR^{12}R^{13}$,



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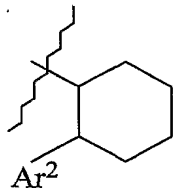

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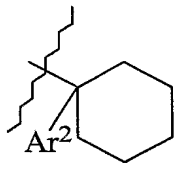

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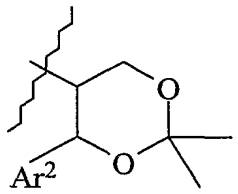

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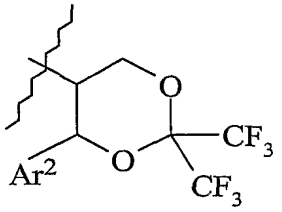


,

wherein p is 0, 1 or 2, Ar^2 is phenyl or pyridyl; and, R^{12} and R^{13} are each independently selected from hydrogen, straight or branched alkyl of up to 6 carbon atoms or cyclic alkyl of between 5 and 7 carbon atoms;

- R^3, R^4 and R^5 are each independently selected from hydrogen and lower alkyl; and
- R^6 is hydrogen, methyl or forms with R^1 a ring of from 3 to 7 carbon atoms which can contain an oxygen or nitrogen atom, or R^1 and R^6 can together be carbonyl;

provided that, when X is –OCO- , then l is 1, 2 or 3 and m is 1.

2. The compound of claim 1, wherein:

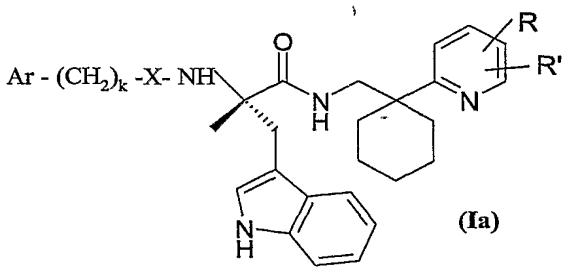
- k is 0 or 1;
- l is 1;
- m is 0 or 1;
- n is 0 or 1;
- X is -CO-, -OCO-, or $-SO_2-$;

- Ar is benzofuryl, furyl, indolyl, isoquinolyl, naphthyl, phenyl, pyridyl, quinolyl or thienyl each unsubstituted or substituted with 1 or 2 substituents selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, - CF_3, - $(CH_2)_qNR^7R^8$, wherein R^7 and R^8 can form a ring of between 5 to 7 atoms which may contain 1 or 2 oxygen or nitrogen atoms, or R^7 and R^8 can be independently selected from hydrogen, straight or branched alkyl of up to 4 carbon atoms or cyclic alkyl of 5 carbon atoms;
- Ar^1 is independently selected from Ar, and can also be pyridyl-*N*-oxide;
- R^1 and R^6 are cyclic alkyl of from 5 to 7 carbon atoms or R^1 and R^6 together are carbonyl;
- R^2 is independently selected from unsubstituted or substituted pyridyl or is hydrogen, hydroxy, alkoxy, -NMe_2, -$CONR^{12}R^{13}$ wherein R^{12} and R^{13} are each independently selected from H and CH_3; and
- R^3, R^4 and R^5 are each independently selected from hydrogen and methyl.

3. The compound of claim 1, wherein:

- l is 1;
- m is 1;
- n is 0;
- R^2 is 2-pyridyl;
- R^6 forms a cyclohexyl with R^1.

4. A compound of formula (Ia):



(Ia)

wherein Ar, k and X have the meanings given in claim 1 and the pyridine ring is optionally substituted by with 1 or 2 substituents, R and R', independently selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, - CF_3, -$(CH_2)_qNR^7R^8$, wherein R^7 and R^8 together with the nitrogen atom to which they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms, or R^7 and R^8 can be independently selected from hydrogen or cyclic alkyl of between 5 to 7 carbon atoms , or a pharmaceutically acceptable salt thereof.

5. The compound of claim 4, wherein Ar is benzofuryl, furyl, indolyl, isoquinolyl, naphthyl, phenyl, pyridyl, quinolyl or thienyl, each unsubstituted or substituted with 1 or 2 substituents selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, - CF_3, -$(CH_2)_qNR^7R^8$, wherein R^7 and R^8 together with the nitrogen atom to which they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms, or R^7 or R^8 can be a independently selected from hydrogen or cyclic alkyl of 5 carbon atoms anx X is –CO-, -OCO- or $–SO_2$.

6. The compound of claim 4 or 5, wherein X is – CO -.

7. The compound of claim 4 or 5, wherein X is –OCO-.

8. The compound of claim 4 or 5, wherein X is - and X is $–SO_2$-.

9. Any of the following compounds or a pharmaceutically acceptable salt thereof:

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-nitro-benzamide;

C-dimethylamino-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

1*H*-indole-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

benzo[b]thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-5-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide; and

1*H*-indole-2-carboxylic acid ((S)-2-(1*H*-indol-3-yl)-1-{[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-carbamoyl}-1-methyl-ethyl)-amide.

10. Any of the following compounds or a pharmaceutically acceptable salt thereof:

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methyl-benzamide;

4-chloro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methoxy-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methanesulfonyl-benzamide;

3-cyano-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

3-chloro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methoxy-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methanesulfonyl-benzamide;

dimethylamino-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methyl-benzamide;

2-chloro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-nitro-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-methoxy-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-methyl-benzamide;

2-fluoro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-tolyl-ethanoylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-o-tolyl-ethanoylamino)-propionamide;

(S)-2-[2-(4-hydroxy-phenyl)-ethanoylamino]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-[2-(3-hydroxy-phenyl)-ethanoylamino]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-m-tolyl-ethanoylamino)-propionamide;

(S)-2-[2-(2-fluoro-phenyl)-ethanoylamino]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-thiophen-3-yl-ethanoylamino)-propionamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-isonicotinamide;

furan-3-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

furan-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

5-methyl-isoxazole-3-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1-methyl-1*H*-pyrrole-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

thiophene-3-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-6-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-5-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-4-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-7-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1-methyl-1*H*-indole-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

benzothiazole-6-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-benzotriazole-5-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

3-methyl-thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

5-methyl-thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

6-methyl-pyridine-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

isoquinoline-3-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

quinoxaline-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

quinoline-8-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

5-phenyl-oxazole-4-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

(S)-3-(1*H*-indol-3-yl)-2-[2-(4-methoxy-phenyl)-ethanoylamino]-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-[2-(4-dimethylamino-phenyl)-ethanoylamino]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-[2-(2-nitro-phenyl)-ethanoylamino]-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-[2-(2-methoxy-phenyl)-ethanoylamino]-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-pyrrol-1-yl-benzamide.

11. Any of the following compounds and pharmaceutically acceptable salts thereof:

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid naphthalen-1-ylmethyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3,4-dichloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-nitro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-trifluoromethyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid quinolin-6-ylmethyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-nitro-benzyl ester; and

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-cyano-benzyl ester.

12. Any of the following compounds and their pharmaceutically acceptable salts:

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3,4-dimethoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid naphthalen-2-ylmethyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid indan-2-yl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-methoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-chloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-fluoro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-chloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-nitro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-methyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-tert-butyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-methoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-trifluoromethyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-ethoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-cyano-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2,4-dichloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-methyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-phenoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-methyl-benzyl ester; and

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2,3-dichloro-benzyl ester.

13. Any of the following compounds and their pharmaceutically acceptable salts:

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-phenylmethanesulfonylamino-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-chloro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(naphthalene-1-sulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(quinoline-8-sulfonylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-trifluoromethyl-benzenesulfonylamino)-propionamide;

(S)-2-(biphenyl-2-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(5-methyl-2-phenoxy-benzenesulfonyl-amino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-*p*-tolyloxy-benzenesulfonylamino)-propionamide.

14. Any of the following compounds and their pharmaceutically acceptable salts:

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(toluene-4-sulfonylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methanesulfonylamino-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-chloro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2,2,2-trifluoro-ethanesulfonylamino)-propionamide;

(S)-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(naphthalene-2-sulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(thiophene-2-sulfonylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(3-nitro-benzenesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(4-nitro-benzenesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(3-trifluoromethyl-benzenesulfonylamino)-propionamide;

(S)-2-(3,4-dichloro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(4-trifluoromethyl-benzenesulfonylamino)-propionamide;

(S)-2-(5-chloro-thiophene-2-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-chloro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(toluene-3-sulfonylamino)-propionamide;

(S)-2-(3,4-dimethoxy-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-cyano-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-cyano-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(5-chloro-1,3-dimethyl-1*H*-pyrazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(benzo[1,2,5]thiadiazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(1-methyl-1*H*-imidazole-4-sulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(benzo[1,2,5]oxadiazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

3-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethylsulfamoyl}-thiophene-2-carboxylic acid methyl ester;

(S)-3-(1*H*-indol-3-yl)-2-(5-isoxazol-3-yl-thiophene-2-sulfonylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(2-nitro-phenylmethanesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-cyano-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(1,2-dimethyl-1*H*-imidazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-(3-methoxy-benzenesulfonylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(8-nitro-naphthalene-1-sulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-chloro-5-nitro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2,4,6-trichloro-benzenesulfonylamino)-propionamide;

(S)-2-(4-chloro-2-nitro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(5-benzenesulfonyl-thiophene-2-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(4-trifluoromethoxy-benzenesulfonylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(5-methyl-2-phenoxy-benzenesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-tolyloxy-benzenesulfonylamino)-propionamide;

2-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethylsulfamoyl}-benzoic acid methyl ester;

(S)-2-(3-chloro-4-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2,5-dichloro-thiophene-3-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-chloro-4-methyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-(2-methoxy-4-methyl-benzenesulfonylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-propionamide;

(S)-2-(5-bromo-6-chloro-pyridine-3-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2,4-dinitro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-(4-methanesulfonyl-benzenesulfonylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-*tert*-butyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2,4-dichloro-5-methyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-chloro-5-trifluoromethyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

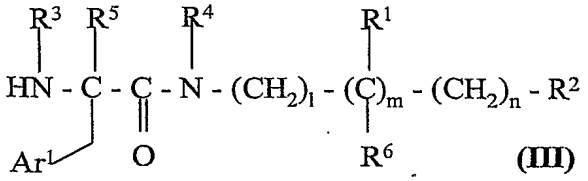
(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(2-nitro-4-trifluoromethyl-benzenesulfonyl-amino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

(S)-2-(4-butyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide.

15. A method for preparing a compound of claim 1, in which X is –CO- prepared by condensing an acid of the formula (II)

$$Ar - (CH_2)_k\text{-}COOH \quad \textbf{(II)}$$

or a derivative thereof with an amine of the formula (III)



(III)

in an aprotic polar solvent in the presence of an appropriate catalyst, the values of the substituents Ar, Ar^1 and R^1 to R^6 and the parameters k to n being as defined in claim 1, with reference to formula (I), and optionally converting the resulting product to a pharmaceutically acceptable salt.

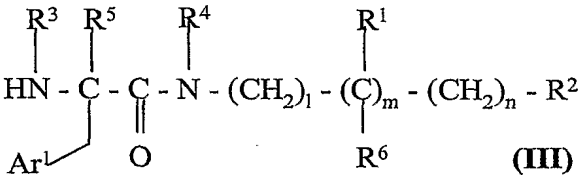
16. The method of claim 15, wherein the condensation is carried out in *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) and *N,N*-diisopropyl-ethylamine (DIPEA).

17. A method for preparing a compound of claim 1, in which X is –OCO-, which comprises:

forming a carbonate from an alcohol of the formula (IV)

$$Ar - (CH_2)_k\text{-}OH \quad \textbf{(IV)}$$

and reacting the carbonate with an amine of the formula (III)



(III)

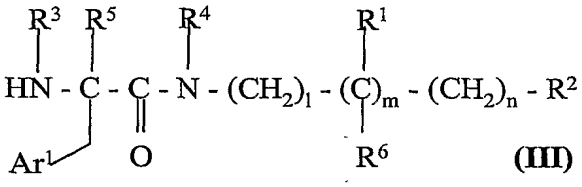
in an aprotic polar solvent in the presence of a base, the values of the substituents Ar, Ar^1 and R^1 to R^6 and the parameters k to n being as defined above with reference to formula (I), and optionally converting the resulting product to a pharmaceutically acceptable salt.

18. The method of claim 17, wherein the compound of formula (IV) is reacted with 4-nitrophenyl chloroformate in dichloromethane in the presence of pyridine, and the resulting carbonate ester is reacted with the amine of formula (III) in dimethyl formamide in the presence of *N,N*-dimethyl-4-amino pyridine.

19. A method of preparing a compound of claim 1 in which X is $–SO_2–$, which comprises condensing a sulfonyl chloride of the formula (V)

$$Ar - (CH_2)_k\text{-}SO_2Cl \quad \textbf{(V)}$$

with an amine of the formula (III)

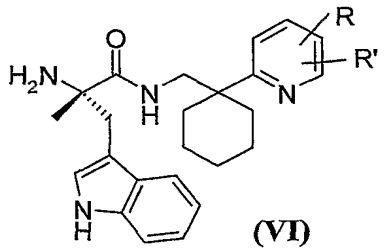


(III)

in an aprotic polar solvent in the presence of a base as catalyst, the values of the substituents Ar, Ar^1 and R^1 to R^6 and the parameters k to n being as defined in claim 1, with reference to formula (I), and optionally converting the resulting product to a pharmaceutically acceptable salt.

20. The method of claim 19, wherein the condensation is carried out in dimethylformamide in the presence of *N,N*-diisopropylethylamine and *N,N*-dimethyl-4-aminopyridine.

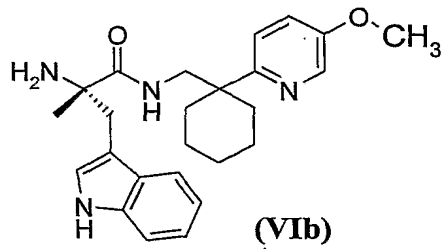
21. The method of any of claims 15-20, wherein the amine of formula (III) is chiral (VI)



(VI)

wherein the pyridine ring is optionally substituted by with 1 or 2 substituents R and R' selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, - CF_3, - $(CH_2)_qNR^7R^8$, wherein R^7 and R^8 together with the nitrogen atom to which they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms, or $R^7$and R^8 can be independently selected from hydrogen or cyclic alkyl of between 5 to 7 carbon atoms.

22. A compound of claim 21, wherein the compound has the formula (VIb)



(VIb)

23. A salt of a compound of any of claims 1-14, wherein said salt is a hydrochloride, mesylate or sulfate.

24. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-14 in combination with a pharmaceutically acceptable carrier.

25. A method of antagonizing the effects of neuromedin B and/or gastrin-releasing peptide at bombesin receptors which comprises administering a compound according to any of claims 1-14 to a patient.

26. A method of treating sexual dysfunction in a male patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to any one of claims 1-14.

27. A method of treating sexual dysfunction in a male patient, characterized by generalized unresponsiveness or ageing-related decline in sexual arousability, in need of said treatment comprising administering a therapeutically effective amount of a compound according to any one of claims 1-14.

28. Use of a compound of any of claims 1-14 in the manufacture of a medicament for preventing or treating sexual dysfunction in male patients.

29. Use of a compound of any of claims 1-14 in the manufacture of a medicament for preventing or treating sexual dysfunction in male patients characterized by generalized unresponsiveness or ageing-related decline in sexual arousability.

30. A method of treating sexual dysfunction in a female patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to any of claims 1-14.

31. A method of treating sexual dysfunction characterized by generalized unresponsiveness or ageing-related decline in sexual arousability in a female patient in need of said treatment, comprising administering a therapeutically effective amount of a compound according to any of claims 1-14.

32. A method of treating sexual dysfunction in a female patient, characterized by hypoactive sexual desire disorders, sexual arousal disorders, orgasmic disorders or anorgasmy, or sexual pain disorders, in need of said treatment comprising administering a therapeutically effective amount of a compound according to any of claims 1-14.

33. Use of a compound of any of claims 1-14 in the manufacture of a medicament for preventing or treating sexual dysfunction in female patients in need of said treatment.

34. Use of a compound of any of claims 1-14 in the manufacture of a medicament for preventing or treating sexual dysfunction characterized by generalized unresponsiveness or ageing-related decline in sexual arousability in a female patient.

35. Use of a compound of any of claims 1-14 in the manufacture of a medicament for preventing or treating sexual dysfunction in female patients characterized by hypoactive sexual desire disorders, sexual arousal disorders, orgasmic disorders or anorgasmy, or sexual pain disorders.

36. A method of treating anxiety and panic disorders, social phobia, depression, psychoses, sleeping disorders, memory impairment, pulmonary hypertension, lung repair and lung development disorders, cancer including prostate cancer and pancreatic

cancer, hepatic porphyria, gastrointestinal secretory disturbances, gastrointestinal disorders including colitis, Crohn's disease and inflammatory bowel disease, emesis, anorexia, pain, seasonal affective disorders, feeding disorders, or pruritus in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to any one of claims 1-14.

37. Use of any compound of any one of claims 1-14 in the manufacture of a medicament for preventing or treating anxiety and panic disorders, social phobia, depression, psychoses, sleeping disorders, memory impairment, pulmonary hypertension, lung repair and lung development disorders, cancer including prostate cancer and pancreatic cancer, hepatic porphyria, gastrointestinal secretory disturbances, gastrointestinal disorders including colitis, Crohn's disease and inflammatory bowel disease, emesis, anorexia, pain, seasonal affective disorders, feeding disorders and pruritus.

38. Use according to any of claims 28, 29, 33, 34, 35 and 37 wherein the medicament is adapted for oral administration.

INTERNATIONAL SEARCH REPORT

Ir al Application No
PCT/EP 01/14401

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 A61K31/4402 A61P15/00 C07D405/14 C07D413/14
C07D409/14 C07D401/14 C07D417/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 07718 A (HORWELL DAVID CHRISTOPHER ;PRITCHARD MARTYN CLIVE (GB); WARNER LAM) 26 February 1998 (1998-02-26) cited in the application examples	1,24-38
X	Scheme 5, compound IX page 42, line 13; examples 12,27	22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2002	02/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	De Jong, B

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,15-20,23-38 (all in part)

Present claims 1,2,15-20,23-38 relate to an extremely large number of possible compounds and the use/preparation of these compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search for claims 1,2,15-20,23-38 has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to claim 3.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/14401

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9807718 A	26-02-1998	AU 733226 B2	10-05-2001
		AU 4146697 A	06-03-1998
		BR 9711342 A	17-08-1999
		EP 0920424 A1	09-06-1999
		JP 2001500850 T	23-01-2001
		NO 990788 A	19-02-1999
		PL 331710 A1	02-08-1999
		TR 9900364 T2	21-05-1999
		WO 9807718 A1	26-02-1998
		US 6194437 B1	27-02-2001
		ZA 9707526 A	19-02-1998